JULY 1973

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American Heart Journal

GEORGE E BURCH *Editor*

HARRY L COLCOLOUGH
JOHN H PHILLIPS *Assistant Editors*

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An international publication for the study of the circulation

Contents on pp 3 5 and 7

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American Heart Journal

An international publication for the study of the circulation

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GEORGE E BURCH M D

Assistant editors
HARRY L COLCOLOUGH M D
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New Orleans Louisiana 70112

Publisher
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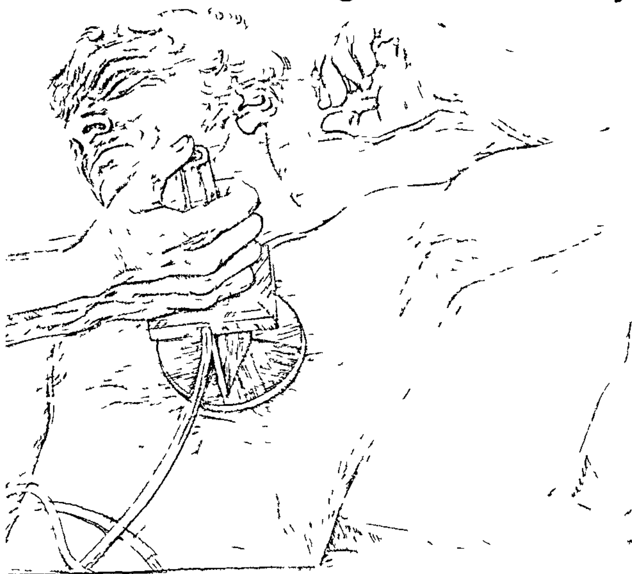
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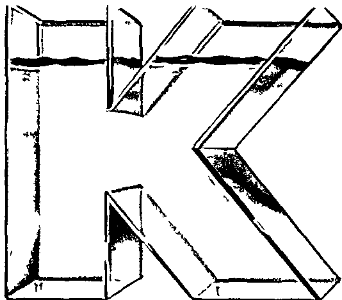
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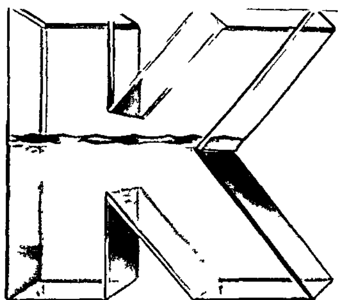
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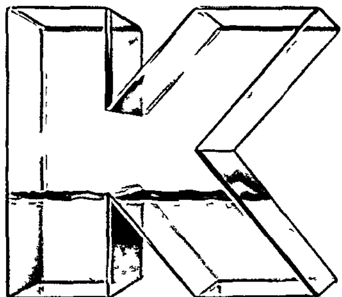
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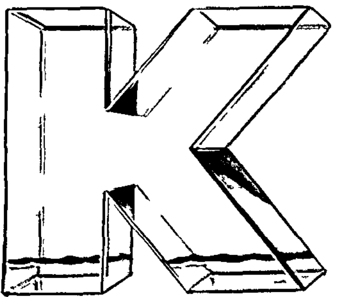
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'Dyrenium' Conserves Potassium add it to the thiazides or furosemide

In the treatment of edema* Dyrenium conserves the potassium most other diuretics waste and augments the action of other diuretics

Before prescribing see complete prescribing information in SK&F literature or *PDR*

Indications **Edema associated with congestive heart failure cirrhosis and nephrotic syndrome steroid-induced edema idiopathic edema edema due to secondary hyperaldosteronism and edema resistant to other diuretic therapy**

Contraindications Severe or progressive kidney disease or dysfunction (possible exception nephrosis) Severe hepatic disease Pre existing elevated serum potassium Hypersensitivity to the drug Continued use in developing hyperkalemia Do not give potassium supplements either by drug or by diet

Warnings Observe regularly for possible blood dyscrasias liver damage or other idiosyncratic reactions Blood dyscrasias have been reported Check BUN and serum potass um periodically especially in the elderly diabetics and those with suspected or confirmed renal insufficiency Use in pregnancy only when essential to patient welfare

Dyrenium (triamterene SK&F) and sp ronolactone are not usually used concurrently if they are however frequent serum potassium determina t ons are required

Precautions If hyperkalem a develops withdraw the drug The following may also occur electrolyte imbalance low salt syndrome (with low salt intake) reversible mild nitrogen retention decreasing alkali reserve with poss ble metabolic acidosis Do periodic hematologic studies in cirrhotics with splenomegaly Concomitant use with antihypertensive drugs may result in an additive hypotensive effect When Dyren um is to be discontinued after intensive or prolonged therapy w th draw gradually because of poss ble rebound kaliuresis

Adverse Reactions Diarrhea nausea and vomiting (may indicate electrolyte imbalance) other gastrointestinal d s turbances weakness headache dry mouth anaphylaxis photosensitivity elevated uric ac d rash

Note When combined with another diuret c the initial dosage of each agent should be lower than recommended

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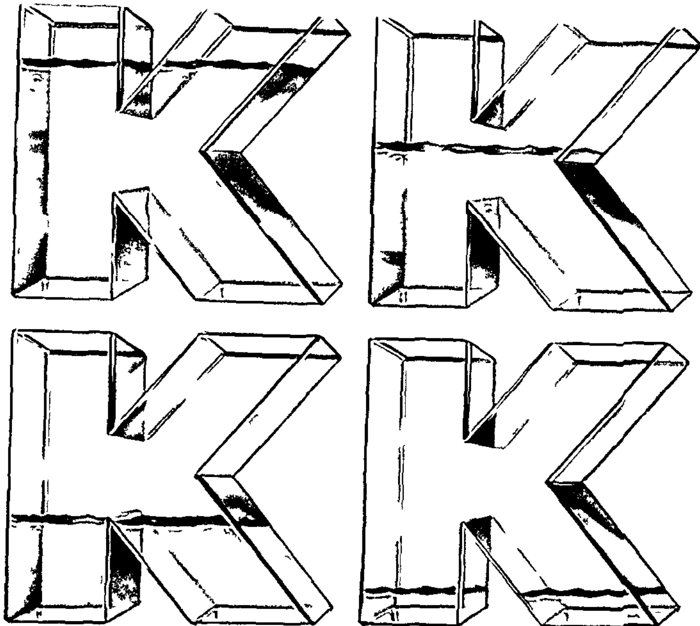
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AUGUST 1973

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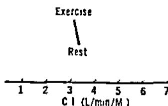
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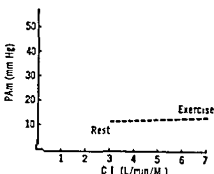
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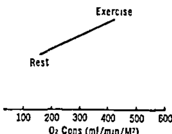
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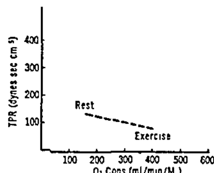


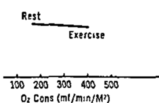
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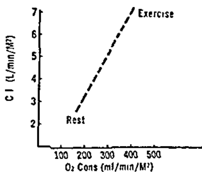


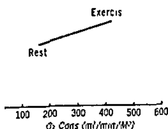
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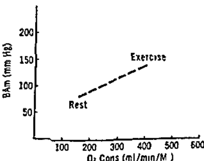


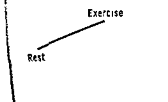
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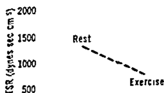


BRACHIAL ARTERY (MEAN PRESSURE)





TOTAL SYSTEMIC RESISTANCE



IN ANGINA PECTORIS

- to abort or terminate acute anginal attacks
- to reduce the frequency and severity of anginal episodes often caused by unavoidable everyday *stress*

ISORDIL SUBLINGUAL
(ISOSORBIDE DINITRATE)

SUBLINGUAL TABLETS 2.5 mg and 5 mg

*Indications Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information FDA has classified the indication as follows
Probably effective When taken by the sublingual route Isordil Sublingual is indicated for the treatment of acute anginal attacks and for prophylaxis in situations likely to provoke such attacks
Final classification of the less than effective indications requires further investigation

Contraindication Idiosyncrasy to this drug

Warnings Data supporting the use of nitrites during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety

Precautions Tolerance to this drug and cross tolerance to other nitrites and nitrates may occur

Adverse Reactions Cutaneous vasodilation with flushing Headache is common and may be severe and persistent Transient episodes of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension may occasionally develop This drug can act as a physiological antagonist to norepinephrine acetylcholine histamine and many other agents An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea vomiting weakness restlessness pallor perspiration and collapse) can occur even with the usual therapeutic dose Alcohol may enhance this effect Drug rash and/or exfoliative dermatitis may occasionally occur

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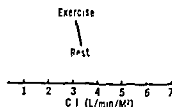
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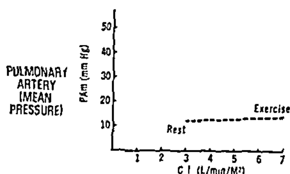
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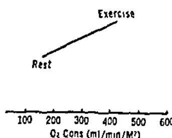
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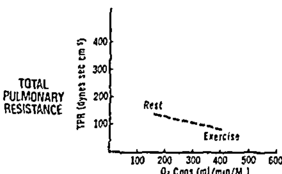
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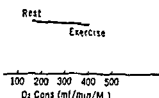
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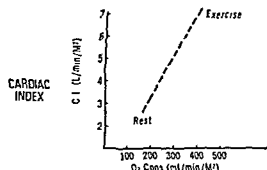


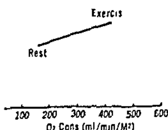


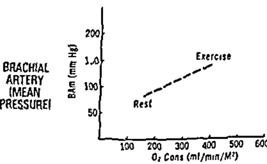


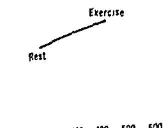


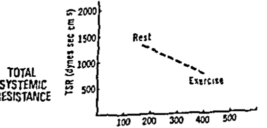












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"The drug of choice for oral replacement of potassium is potassium chloride solution."

AMA Drug Evaluation 1971 First Edition
Chicago American Medical Association p 121

Kay Ciel® Elixir is potassium chloride... tastes good too!

COMPOSITION Each 15 cc (one tablespoonful) contains potassium chloride 1 5 Gm supplying 20 mEq of elemental potassium in a cherry flavored palatable *base alcohol 4 Contains no sugar*
INDICATIONS Treatment of potassium deficiency occurring especially during thiazide diuretic or corticosteroid therapy digitalis intoxication low dietary intake of potassium or as a result of excessive vomiting and diarrhea
CONTRAINDICATIONS Impaired renal function untreated Addison s Disease dehydration heat cramps and hyperkalemia
PRECAUTIONS Potassium chloride should be administered *with caution and* adjusted to the requirements of the indi*vidual patient since the amount of def*iciency and corresponding daily dose is often not known Excessive or even therapeutic dosages may result in potassium intoxication *Patients should be frequently* checked and periodic ECG and/or plasma *potassium levels made High plasma con*centrations of potassium ion may cause cardiac depression arrhythmias or arrest Use with caution in patients with cardiac disease In hypokalemic states attention *should be directed toward the correction* of the frequently associated hypochloremic alkalosis
SIDE EFFECTS Vomiting nausea abdominal discomfort and diarrhea may occur Symptoms and signs of potassium intoxication include listlessness mental *confusion paresthesia of the extremities* weakness of the legs flaccid paralysis fall in blood pressure cardiac arrhythmias and heart block When hyperkalemia exists it should be promptly treated with the discontinuance of potassium adminis*tration or other steps to lower serum levels* if indicated since sudden shift in plasma *levels may induce potentially dangerous* cardiac arrhythmias
DOSAGE AND ADMINISTRATION Adults one tablespoonful (15 cc) diluted in one glass of water twice daily after the *morning and evening meal* Larger dose may be indicated according to the individual patient s requirements but should be administered under close supervision due to the possibility of potassium intoxication *Patients should be cautioned to* follow directions explicitly in regard to *dilution of Kay Ciel Elixir to prevent* gastrointestinal injury
HOW SUPPLIED One pint and one gallon bottles

Cooper
Cooper Laboratories Inc Wayne N J *07470/Ste Therese P Q Canada*

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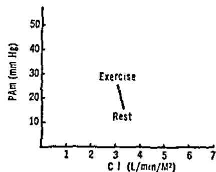
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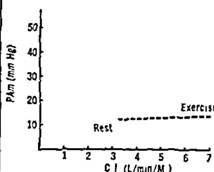
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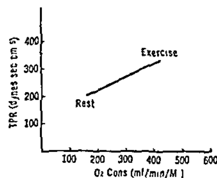
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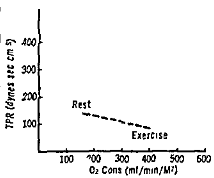


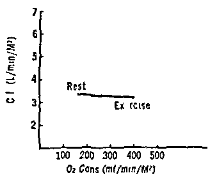
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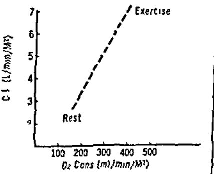


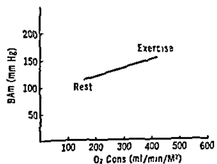
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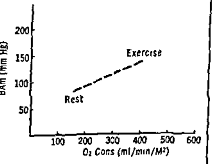


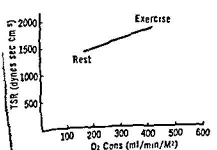
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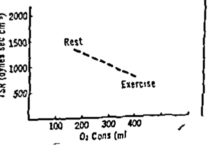


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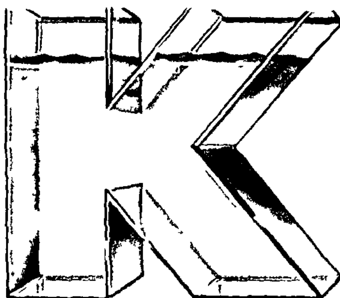
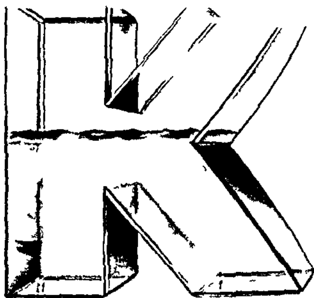
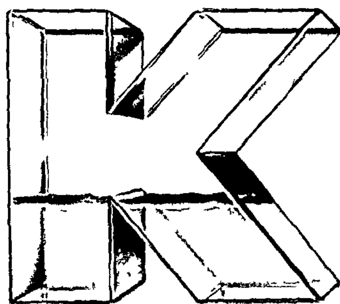
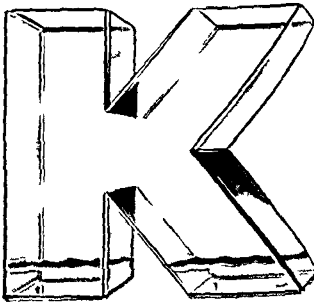
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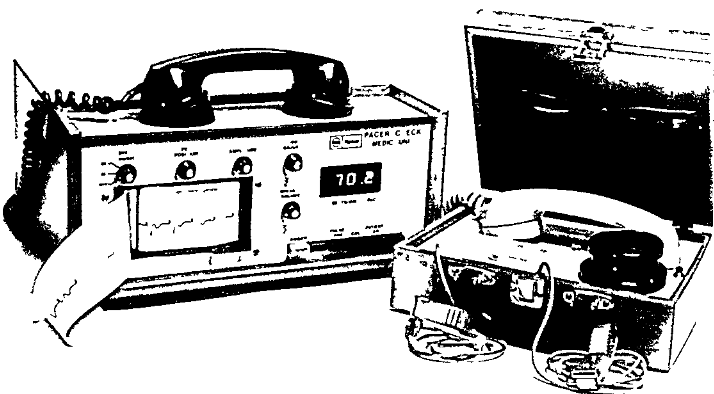
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July 1973 Volume 86 Number 1

Editorial

Dietary treatment of renal failure

*David S David M D**
New York N Y

In order for medicine to become a science one must attempt to quantitate This is one of the many pearls of wisdom taught to me by the late Professor David Seegal in medical school Although nephrology is far from being a true science there are many parameters which are readily measurable—i e weight intake and output serum and urinary electrolytes creatinine clearance etc Furthermore the nephrologist has at his disposal the ability to replace or replenish quantitatively any losses of fluids and electrolytes and with diuretics and dialysis the means to rid the body of any excesses of fluids and electrolytes In other words the physician taking care of the patient with renal failure has the ability to regulate and take over through dietary means many of the kidney s normal functions It is important for all physicians to master this skill because of the new hope that dialysis and transplantation have offered in prolonging and improving the quality of life of patients with renal failure

Methods

Protein Since one of the main sources of uremic toxins contributing to the uremic syndrome is the protein in the diet the intake of protein has to be restricted In patients with chronic renal disease protein restriction usually need not be imposed until the creatinine clearance falls below 10 to 15 cc per minute Certain patients with renal disease who have associated catabolic states (postoperative infection and fever) excess non-dietary sources of protein (gastrointestinal bleeding) and low flow states (congestive heart failure dehydration) may develop uremic symptoms at higher creatinine clearances and thereby will require protein restriction earlier But it is important to note that patients with azotemia secondary to low flow states alone (without significant underlying renal disease) such as is commonly seen in congestive heart failure[1] rarely develop uremic symptoms requiring protein restriction and their azotemia responds very well to the therapy of the underlying disease

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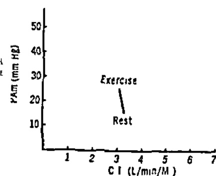
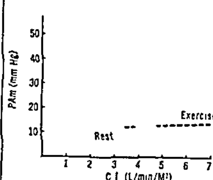
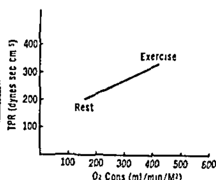
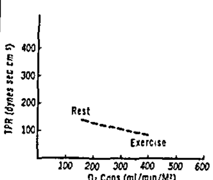
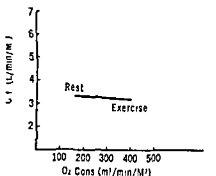
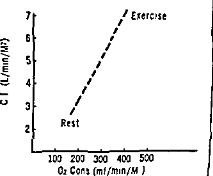
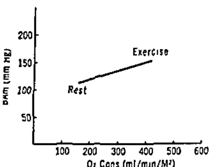
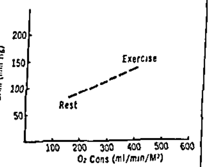
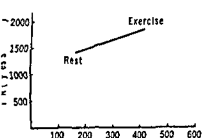
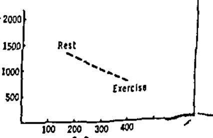
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Dietary treatment of renal failure

*David S David M D**
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culation to the liver, which then synthesizes the non essential amino acids The diet then need provide only the essential amino acids, and its protein content can be restricted to 0 3 to 0 5 Gm per kilogram of body weight[4,5] Egg chicken, beef steak and lamb, because of their high biological value, constitute the main proteins allowed in the diet[5,6]

The success of the Giovannetti diet, like any other diet depends on whether the patient adheres to it or not There is one very important factor that the physician has under his control that will insure the success of the diet This is to get a knowledgeable dietician to sit down with the patient and his family and go over the patient's likes and dislikes and tailor make a weekly menu with sufficient variety that will keep the patient satisfied Many companies now have available a variety of low protein flour, recipes and ready made foods for these patients When this is done, the diet can be quite tolerable despite its restrictions and most patients will abide by it because it makes them feel better Most failures on the diet under these circumstances are due to progression of the renal disease to a point where diet alone cannot manage the symptoms and dialysis becomes necessary This usually occurs at creatinine clearances less than 3 c c per minute

So far the emphasis has been on protein restriction But it is extremely important to remember that the patient must get sufficient protein in the diet to maintain nitrogen balance Otherwise he will break down his own body protein and will get a clinical picture similar to Kwashiorkor[8-11] with increased susceptibility to infection cardiomyopathy and a rapid downhill course Therefore patients who have excessive losses of protein such as nephrotics or patients undergoing dialysis catobolic patients and patients on broad spectrum antibiotics may require greater amounts of protein in the diet to maintain nitrogen balance[1-13]

Carbohydrates If the Giovannetti diet is to maintain good nitrogen balance, it must provide adequate calories in the form of carbohydrates The carbohydrates prevent the breakdown of body protein as an energy source and, by stimulating insulin secretion, enhance the proper utilization of the essential amino acids Two well known clinical observations that at first seem paradoxical but are readily explainable are, firstly, that diabetic patients who are on insulin or oral hypoglycemic agents require less of these medications after they develop renal failure, and secondly, that non diabetic patients who develop renal failure have a very high incidence of glucose intolerance resembling that seen in maturity onset diabetes Since about 50 per cent of the plasma insulin is used and degraded by the kidney[14] the insulin half life is prolonged in patients with renal failure thus explaining the decrease in insulin requirements in diabetic patients who develop renal failure It has also been demonstrated that there is a peripheral insensitivity to endogenous insulin in patients with renal failure,[15,16] thus explaining the abnormal glucose tolerance in non diabetic patients who develop renal failure

These abnormalities in carbohydrate metabolism have some important clinical implications The physician should be aware of the potential hazard of hypoglycemia in any diabetic patient who is on a fixed dose of hypoglycemic agents in whom renal insufficiency develops In the emergency treatment of hyperkalemia the normal dose of insulin/glucose given intravenously is 1 unit of regular insulin per 4 Gm glucose To avoid delayed hypoglycemic reactions secondary to the prolonged half life of insulin in patients with severe renal insufficiency the insulin/glucose ratio should be 1 unit of insulin per 10 Gm glucose[12] Rarely rebound hypoglycemia and occasionally severe hyperglycemia with hyperosmolar coma have been reported in patients undergoing dialysis[17-19]

Lipids Hyperlipemia is a well known consequence of the nephrotic syndrome with or without renal failure More recently it has been shown that patients with non nephrotic uremia also have hypertriglyceridemia[20,21] The exact mechanism for this is unknown but may be related to decreased tissue lipoprotein lipase and trigyceride removal capacity[20] Hemodialysis seems to accentuate the hyperlipemia both acutely and chronically[21,22] In general dietary

control and anti hyperlipidemic drugs are ineffective but a trial of both regimens should be attempted in every patient

Fluids Any patient with renal failure should receive the maximum amount of fluid per 24 hours that his kidneys can excrete without developing evidence of congestion or edema The reason for this is that urea and possibly other toxic metabolic products back diffuse into the blood throughout the length of the tubules An increase in urine flow through the tubule (increase in free water clearance) will increase the amount of these products excreted, since they would have less time to back diffuse into the blood [12]

To determine the ideal amount of fluid per 24 hours for any given patient body weight and fluid intake and output must be recorded daily The physical exam and frequent monitoring of vital signs are extremely important in following the patient s state of hydration [1] Changes in heart size on serial chest x rays are quite valuable Where the signs and symptoms are equivocal a blood volume determination may be helpful Once it is felt by all the clinical and other diagnostic parameters that the patient is at his ideal state of hydration the total fluids per 24 hours to be given equals the maximum urine output plus any other measurable losses plus 400 to 600 c c for insensible fluid loss [12]

About 50 per cent of patients with renal failure on the Giovannetti diet retain water in spite of all restrictions placed on them so diuretics need to be used Because of their very low glomerular filtration rates only the very potent diuretics such as furosemide (Lasix) *will be effective* The dose can be increased until the desired diuretic effect is achieved which may be as much as 2 to 3 Gm of furosemide per day in divided doses [12]

It is extremely important to stress the fact that there is no indication for digitalis in patients with congestion secondary to hypervolemia alone in renal failure [1] If any thing this drug is contraindicated *in the e* patients because of its accumulation to toxic levels in renal failure and because of the marked fluctuations in serum potassium that can occur in the course of treating these patients with diuretics and dialysis Fluid restriction diuretics and dialysis are the only proven safe methods of treating the congested state in these patients [1] When digitalis must be used in patients with advanced renal failure (for therapy of severe arrhythmias or associated heart failure that cannot be managed by control of fluid volume alone) digitoxin is the drug of choice [24]

Sodium Unlike patients with congestive heart failure who always tend to have severe sodium retention excreting less than 10 mEq per liter of urine patients with renal failure tend to lose more sodium This will vary from patient to patient at the same glomerular filtration rate depending on the underlying renal disease—i e patients with tubular involvement such as pyelonephritis will lose more sodium than patients with glomerulonephritis The sodium loss will also vary in the same patient at different levels of renal function Therefore since the patient s kidneys have lost their ability to significantly regulate the amount of sodium excreted per 24 hours they are all potentially salt losers or salt retainers depending on whether the dietary sodium is less or greater than the amount excreted The implications of these are obvious too much sodium in the diet can contribute to or aggravate the patient s hypertension and congestion too little sodium may result in muscle cramps convulsions hypovolemia hypotension and further deterioration of renal function [12] To calculate the amount of sodium to be allowed in the diet one needs to know the 24 hour urinary sodium loss If renal function is not stable as in the diuretic phase of acute renal failure or if there are extrarenal losses of sodium such as vomiting the 24 hour urinary sodium and other sodium losses must be measured every day and the intake adjusted accordingly

The treatment of sodium deficiency is easy with increase of replacement therapy In patients who are sodium retainers diuretics may have to be used Salt substitutes need careful handling in renal failure patients since the cation substituted is potassium and each packet (1 Gm weight) has about 12 mEq potassium [12]

Potassium Hyperkalemia is a common problem in severe renal insufficiency often aggravated by the associated acidosis The

amount of potassium to be allowed in the diet in any given patient can be estimated by the 24 hour urinary potassium If, despite all restriction the patient still tends to be hyperkalemic, exchange resins can be given orally If a sodium exchange resin (exchanging about 2 to 3 mEq sodium per Gm resin[12]) is used, one may run into problems with sodium retention and edema Calcium and aluminum resins have also been used but the former can cause hyper calcemia[25, 26] and aluminum intoxication has been reported with the latter [27, 29]

The emergency treatment of life threat ening hyperkalemia[25, 6] consists of intra venous glucose and insulin (10 Gm glucose per 1 unit regular insulin) calcium sodium bicarbonate and hypertonic saline solution Since most patients with renal failure are hypervolemic sodium bicarbonate and saline cannot be given safely In general I have found that 5 units of regular insulin given intravenously followed by a bolus of 50 c c of 50 per cent dextrose and an intra venous drip of 500 c c of 10 per cent dex trose in water containing 5 Gm of calcium gluconate run at 100 c c per hour will bring the serum potassium down immediately and protect the patient from the cardio vascular effects of hyperkalemia until the oral exchange resins or enemas begin to take effect [12]

Hypokalemia may be seen at any stage of renal failure and should be treated be cause of its long term adverse effects on the kidney But the replacement therapy must be slow and serum potassium must be care fully monitored since it takes several hours for the extracellular potassium to come into complete equilibration with the intracel lular pool [12] If potassium sparing diuretics are to be used potassium supplements must be stopped [1]

Acidosis Most patients with severe renal failure have some degree of compensated metabolic acidosis The use of the oral phosphate binding gels tends to partially alleviate this Since sodium and magnesium may be retained in renal failure antacids that are low in these cations are preferred Some workers have used calcium carbo nate[30] as an antacid in those patients who have a low serum calcium and severe renal osteodystrophy The main complication of this form of therapy is hypercalcemia [31]

In severe decompensated metabolic acido sis, intravenous sodium bicarbonate may be used if the patient can tolerate the sodium load In patients with extensive tubular involvement that wastes a great deal of bicarbonate sodium in the diet can be restricted and sodium bicarbonate tablets can be used as supplements for con trol of the acidosis [12]

Since lactate is normally converted to bicarbonate by the liver one must be care ful in the use of any intravenous or peri toneal dialysis solutions which contain lactate as the main buffer in patients with associated lactic acidosis and/or severe liver disease It is contraindicated in the former and when it is used in patients with liver disease arterial pH should be checked early in the course of therapy to ensure the acidosis is being corrected rather than made worse [12]

Minerals and vitamins Since the dietary intake may vary in patients with renal failure, and since water soluble vitamins may be removed during dialysis [1, 3, 35] the water soluble vitamins should be given as supplements to all patients with renal fail ure Patients who are hypocalcemic with raised alkaline phosphatases and radio graphic evidence of severe renal osteo dystrophy may be tried on vitamin D or its more active metabolites such as 25 hydroxycholecalciferol [12] But this is to be done under close supervision since hyper calcemia and severe soft tissue calcification may occur as a result of therapy [36]

Since the serum magnesium levels in most patients with advanced renal failure is normal or high irrespective of the intra cellular magnesium one usually tries to avoid large doses of magnesium in the form of antacids or laxatives [12]

In general the anemia of patients with renal failure is not associated with signifi cant iron deficiency in spite of the poor absorption of oral iron in these patients [12] But some patients on chronic hemodialysis become iron deficient because of frequent venepuncture and blood loss in the coil and here supplemental iron therapy be comes necessary [12]

I would like to thank Dr Albert Rubin and Dr Paul Bienstock for their advice and guidance in preparing the manuscript

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amount of potassium to be allowed in the diet *in any given patient can be estimated* by the 24 hour urinary potassium. If, despite all restriction, the patient still tends to be hyperkalemic exchange resins can be given orally. If a sodium exchange resin (exchanging about 2 to 3 mEq sodium per Gm resin[12]) is used, one may run into problems with sodium retention and edema. Calcium and aluminum resins have also been used, but the former can cause hypercalcemia[25,26] and aluminum intoxication has been reported with the latter.[27,9]

The *emergency treatment of life threatening* hyperkalemia[25,26] consists of intravenous glucose and insulin (10 Gm glucose per 1 unit regular insulin), calcium, sodium bicarbonate and hypertonic saline solution. Since *most patients with renal failure are* hypervolemic, sodium bicarbonate and saline cannot be given safely. In general I have found that 5 units of regular insulin given intravenously followed by a bolus of 50 c.c. of 50 per cent dextrose and an intravenous drip of 500 c.c. of 10 per cent dextrose in water containing 5 Gm. of calcium gluconate run at 100 c.c. per hour will bring the serum potassium down immediately and protect the patient from the cardiovascular effects of hyperkalemia until the *oral exchange resins or enemas begin to* take effect.[12]

Hypokalemia may be seen at any stage of renal failure and should be treated because of its long term adverse effects on the kidney. *But the replacement therapy must* be slow and serum potassium must be carefully monitored since it takes several hours for the extracellular potassium to come into complete equilibration with the intracellular pool.[12] *If potassium sparing* diuretics are to be used, potassium supplements must be stopped.[12]

Acidosis. Most patients with severe renal failure have some degree of compensated metabolic acidosis. The use of the oral phosphate binding gels tends to partially alleviate this. Since sodium and magnesium may be retained in renal failure, antacids that are low in these cations are preferred. *Some workers have* used calcium carbonate[30] as an antacid in those patients who have a low serum calcium and severe renal osteodystrophy. The main complication of this form of therapy is hypercalcemia.[31]

In severe decompensated metabolic acidosis, intravenous sodium bicarbonate may be used if the patient can tolerate the sodium load. In patients with extensive tubular involvement that wastes a great deal of bicarbonate, sodium in the diet can be restricted and sodium bicarbonate tablets can be used as supplements for control of the *acidosis*.[12]

Since lactate is normally converted to bicarbonate by the liver, one must be careful in the use of any intravenous or peritoneal dialysis solutions which contain *lactate as the main buffer in patients with* associated lactic acidosis and/or severe liver disease. It is contraindicated in the former and when it is used in patients with liver disease arterial pH should be checked early *in the course of therapy* to ensure the acidosis is being corrected rather than made worse.[12]

Minerals and vitamins. Since the dietary intake may vary in patients with renal failure, and since water soluble vitamins may be removed during dialysis,[1,32,35] the water soluble vitamins should be given as supplements to all patients with renal failure. Patients who are hypocalcemic with raised alkaline phosphatases and radiographic evidence of severe renal osteodystrophy may be tried on vitamin D or its more active metabolites such as 25 hydroxycholecalciferol.[12] But this is to be done under close supervision since hypercalcemia and severe soft tissue calcification may occur *as a result of therapy*.[36]

Since the serum magnesium levels in most patients with advanced renal failure is normal or high irrespective of the intracellular magnesium, one usually tries to avoid large doses of magnesium in the form of antacids or laxatives.[12]

In general the anemia of patients with renal failure is not associated with significant iron deficiency in spite of the poor absorption of oral iron in these patients.[1] But some patients on chronic hemodialysis become iron deficient because of frequent venepuncture *and blood loss in the coil* and here supplemental iron therapy becomes necessary.[12]

I would like to thank Dr. Albert Rubin and Dr. Paul Bienstock *for their advice and guidance in* preparing the manuscript.

participant in the study. In addition, all infants with congenital heart disease who died and who did not have cardiac catheterization or cardiac surgery also entered the study. A total of 262 infants satisfied these criteria in the years 1969 and 1970.

Each of the 5 diagnostic centers was visited by one of the authors (George Kelso). Patients were identified from catheterization, autopsy, or surgical log books and from card indexes in the medical record libraries. More detailed information was then obtained from cardiac catheterization, surgical, and autopsy reports. Follow-up information was abstracted from hospital records. The total births for the years 1969 and 1970 was furnished by the State Department of Health. All patients were also identified by county of residence. The data were punched on 50 column IBM computer cards and were processed by means of a card sorter.

Results

A. Incidence. The total number of infants entering the study was 262, giving a calculated incidence of 1.7/1,000 births. The predicted incidence at 2/1,000 births is 304 infants. Therefore, 86 per cent of the infants estimated to be at risk were identified in the 5 centers. Forty-two per cent of the infants were cared for at Milwaukee Children's Hospital, 29 per cent at St. Mary's Hospital, 18 per cent at University Hospital, 6 per cent at Gunderson Clinic, and 5 per cent at Marshfield Clinic. Eighty-nine per cent of the infants were seen at hospitals closely affiliated with a medical school. This information is shown in Table I. Table I also gives the criteria used to admit a patient to the study (catheterization, surgery without prior catheterization, or autopsy). It is seen that 73 per cent (192) of the infants were identified primarily by cardiac catheterization. Twenty-one per cent (53) of the patients died prior to any diagnostic or therapeutic intervention and were admitted to the study on the basis of autopsy findings. Seventeen patients had surgery without any prior catheterization. All of these infants were from the same institution and 16/17 were premature infants who had ligation of a patent ductus arteriosus.

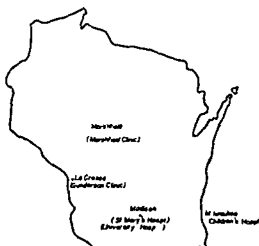


Fig. 1. Map of Wisconsin giving the locations of the 5 centers caring for infants with critical congenital heart disease.

B. Frequency of specific lesions. The most commonly encountered anomaly was ventricular septal defect (VSD) (19 per cent), followed by transposition of the great arteries (TGA) (13 per cent) and patent ductus arteriosus (PDA) (11 per cent). Other frequently seen lesions were hypoplastic left heart syndrome, tetralogy of Fallot, coarctation of the aorta, total anomalous pulmonary venous drainage, and pulmonary valve obstructions—stenosis and atresia. More than one fifth of the patients fell into the "other" category, which included the less common problems, patients with multiple congenital anomalies, and genetic disorders. In those patients where more than one lesion existed, the most important anatomic abnormality was used as a basis for the classification. This material is summarized in Table II.

C. Age first identified. The age range at which these infants were first identified is given in Table III. Twenty-seven per cent (69) were seen during the first week of life, forty-eight per cent (125) by the first month, and seventy per cent (182) by the first 3 months. By 6 months of age, 87 per cent of the patients had been identified. Certain lesions resulted in significant signs and symptoms earlier than others. Thus, 93 per cent of the patients with hypoplastic left heart syndrome, 61 per cent of those with transposition, 58 per cent of the infants with aortic coarctation, and 54 per

Clinical communications

Demography of critical congenital heart disease

*George F Kelso, B S**
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David Z Friedberg M D
Milwaukee, Wisc

Aggressive medical and surgical intervention is the accepted mode of therapy for critically ill infants with congenital heart disease[1,3] Without such intervention it has been demonstrated that 2/1 000 live born infants will die during the first year of life due to congenital cardiac anomalies[4,5] This group of infants can be considered to have "critical congenital heart disease The salvage of these infants thus becomes dependent on early identification (usually in the neonatal period) and subsequent referral to centers having specialized facilities for diagnosis and treatment

The State of Wisconsin with a population of 4,417 731 (1970 census) has a large urban area in its southeast portion (Milwaukee and vicinity) but is otherwise composed of rural farming areas Only five medical facilities in this state care for infants with congenital heart disease They are (1) Milwaukee Children s Hospital Milwaukee–the pediatric teaching unit of The Medical College of Wisconsin (2) University Hospital Madison—the pediatric teaching unit of The University of Wisconsin Medical School (3) St Mary s Medical Center, Madison—a private institution affiliated with The University of Wisconsin (4) Marshfield Clinic Marshfield—a large multi specialty private clinic, and (5) Gunderson Clinic La Crosse—an other large multi specialty private clinic The location of these centers is seen on the map in Fig 1 As far as can be determined, *no other facility in the state cares for infants with critical congenital heart disease*

It was the purpose of this study (1) to identify all infants with critical congenital heart disease who were born in Wisconsin in 1969 and 1970 and to compare this incidence with that predicted from the literature (2) to provide information on the frequency of specific lesions on the age of the patient at the time of diagnostic or therapeutic intervention the mode of therapy (medical or surgical) and the final outcome of this group of infants (3) to follow these children for at least 1 year, and (4) to analyze the referral patterns of these infants in the State of Wisconsin

Material and methods

Any infant under 1 year of age who had congenital heart disease and whose clinical state was such that cardiac catheterization and/or surgery was performed became a

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participant in the study In addition all infants with congenital heart disease who died and who did not have cardiac catheterization or cardiac surgery also entered the study A total of 262 infants satisfied these criteria in the years 1969 and 1970

Each of the 5 diagnostic centers was visited by one of the authors (George Kelso) Patients were identified from catheterization autopsy or surgical log books and from card indexes in the medical record libraries More detailed information was then obtained from cardiac catheterization surgical and autopsy reports Follow up information was abstracted from hospital records The total births for the years 1969 and 1970 was furnished by the State Department of Health All patients were also identified by county of residence The data were punched on 50 column IBM computer cards and were processed by means of a card sorter

Results

A Incidence The total number of infants entering the study was 262 giving a calculated incidence of 1 7/1 000 births The predicted incidence at 2/1 000 births is 304 infants Therefore 86 per cent of the infants estimated to be at risk were identified in the 5 centers Forty two per cent of the infants were cared for at Milwaukee Children s Hospital 29 per cent at St Mary s Hospital 18 per cent at University Hospital 6 per cent at Gunderson Clinic and 5 per cent at Marshfield Clinic Eighty nine per cent of the infants were seen at hospitals closely affiliated with a medical school This information is shown in *Table I* Table I also gives the criteria used to admit a patient to the study (catheterization surgery without prior catheterization or autopsy) It is seen that 73 per cent (197) of the infants were identified primarily by cardiac catheterization Twenty one per cent (53) of the patients died prior to any diagnostic or therapeutic intervention and were admitted to the study on the basis of autopsy findings Seventeen patients had surgery without any prior catheterization All of these infants were from the same institution and 16/17 were premature infants who had ligation of a patent d[illegible]rteriosus

Fig 1 Map of Wisconsin giving the locations of the 5 centers caring for infants with critical congenital heart disease

B Frequency of specific lesions The most commonly encountered anomaly was ventricular septal defect (VSD) (19 per cent) followed by transposition of the great arteries (TGA) (13 per cent) and patent ductus arteriosus (PDA) (11 per cent) Other frequently seen lesions were hypoplastic left heart syndrome tetralogy of Fallot coarctation of the aorta total anomalous pulmonary venous drainage and pulmonary valve obstructions—stenosis and atresia More than one fifth of the patients fell into the other category which included the less common problems patients with multiple congenital anomalies and genetic disorders In those patients where more than one lesion existed the most important anatomic abnormality was used as a basis for the classification This material is summarized in Table II

C Age first identified The age range at which these infants were first identified is given in Table III Twenty seven per cent (69) were seen during the first week of life forty-eight per cent (125) by the first month and seventy per cent (182) by the first 3 months By 6 months of age 87 per cent of the patients had been identified Certain lesions resulted in significant signs and symptoms earlier than others Thus 93 per cent of the patients with hypoplastic left heart syndrome 61 per cent of those with transposition 58 per cent of the infants with aortic coarctation and 54 per

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Table III *Age at which lesion was first identified in 262 patients*

LESION	NUMBER OF PATIENTS	<1 WK	1-4 WKS	1-3 MOS	3-6 MOS	6-12 MOS
VSD	49	5	11	12	14	7
Transposition	33	11	9	8	1	4
Patent Ductus Arteriosus	28	5	9	6	6	2
Hypoplastic Left Heart	26	20	5	0	1	0
Tetralogy of Fallot	23	2	5	6	6	4
Coarctation of Aorta	19	4	7	1	4	3
Total Anomalous Pul Vn	11	1	1	6	2	1
Pulmonary Atresia	7	3	0	3	0	1
Pulmonary Stenosis	7	2	2	1	0	2
Other	59	16	7	14	12	10
TOTAL	262	69 (27%)	56 (21%)	57 (22%)	46 (17%)	34 (13%)

Table IV *Number and per cent of patients surviving out of 262 patients*

LESION	No PTS	No PTS − AUT	No SURVIVING	% SURVIVING	% SURVIVING − AUT
Vent Septal Defect	49	42	40 (M 17, S 23)	82	95
Transposition	33	29	12 (M 6, S 6)	36	41
Patent Ductus	28	25	21 (M 1, S 20)	75	84
Hypoplastic LH	26	11	0 (M 0, S 0)	0	0
Tetralogy	23	21	14 (M 8, S 6)	61	67
Coarctation	19	16	12 (M 6, S 6)	63	75
Tot An Pul Vn	11	8	5 (M 3, S 2)	45	63
Pul Atresia	7	6	2 (M 0, S 2)	29	33
Pul Stenosis	7	7	7 (M 2, S 5)	100	100
Other	59	44	26 (M 19, S 7)	45	60
TOTAL	262	209	139 (M 64 62, S 75 77)	54%	66%

M Medical Follow
S Surgical Follow

died Fifty three of these died before cardiac catheterization or surgery was performed Thirteen patients died within 24 hours of cardiac catheterization This represented a total catheterization mortality rate of 6 8 per cent Approximately equal numbers of patients who were followed medically (25) and surgically (32) succumbed Results are summarized in Table V

F Surgery There were 109 surgical procedures In those situations where more than one surgical procedure was done during the same operation the primary pro

Table I Incidence of critical congenital heart disease

INSTITUTION	No PATIENTS	CRITERIA FOR IDENTIFICATION CATH	AUTOPSY	SURGERY
Milw Child Hosp	112 (42 %)	89	33	—
St Mary's Hosp	77 (29 %)	49	11	17
University Hosp	44 (18 %)	33	11	—
Gunderson Clinic	15 (6 %)	11	4	—
Marshfield Clinic	14 (5 %)	10	4	—
TOTAL	262	192 (73%)	53 (21%)	17 (6%)
PREDICTED (2/1000)	304			

Table II Frequency of specific lesions in 262 patients

LESION	NUMBER OF PATIENTS	PERCENT OF TOTAL
Ventricular Septal Defect	49	19 %
Transposition	33	13 %
Patent Ductus Arteriosus	28	11 %
Hypoplastic Left Heart	26	10 %
Tetralogy of Fallot	23	9 %
Coarctation of Aorta	19	7 %
Total Anomalous Pul Vn	11	4 %
Pulmonary Atresia - Intact Septum	7	—
Pulmonary Stenosis	7	—
Other	59	22 %
TOTAL	262	

cent having patent ductus arteriosus were seen during the first month of life This was in contrast to patients with tetralogy of Fallot, total anomalous pulmonary venous return, and ventricular septal defect—the majority of whom were identified after the first month of life

D Survival At the end of at least 1 year of follow up 54 per cent of patients (139) were alive However, if we eliminate the 53 patients who entered the study by autopsy without the benefit of catheterization and further surgical therapy the survival rate rises to 66 per cent Of the 139 patients surviving 45 per cent (62) were treated medically while 55 per cent (77) had surgery The best salvage was seen in patients with pulmonary stenosis (100 per cent) VSD (82 per cent) PDA (75 per cent) coarctation (63 per cent) and tetralogy of Fallot (61 per cent) If patients entering the study by autopsy are eliminated, then salvage rates go up to 95 per cent in VSD, 84 per cent in PDA 75 per cent in coarctation and 67 per cent in tetralogy of Fallot No patients with hypoplastic left heart survived—none had surgery The salvage in transposition of the great arteries was disappointing (36 per cent) This information is seen in Table IV

E Deaths At the end of 1 year of follow up 46 per cent of the patients 123) had

referral thus becomes obvious It is in this area that we feel progress can be made in reducing the over all mortality rate of infants with critical congenital heart disease

The frequency of specific lesions agrees quite well with that of other studies[2 6 7] The small variations are in part due to the fact that we chose to examine the first year of life while others[2 7] have concentrated on the first month only This would obviously skew the diagnostic incidence towards the lesions whose life threatening characteristics became apparent earlier—i e transposition pulmonary atresia and aortic coarctation As has been mentioned the increased number of patients with patent ductus arteriosus relates to the fact that one institution was very interested in the ductus arteriosus of the premature and tended to be more aggressive in its diagnosis and treatment If these patients were excluded patent ductus arteriosus would then comprise only 6 per cent of the total

In a recent study by Feldt and associates[4] 43 5 per cent of the patients were diagnosed within the first week of life as opposed to 27 per cent of our patients The Feldt study only included the surrounding county whereas we were concerned with an entire state It is quite possible that the distance from hospital of birth to referring center was sufficient to delay referral Again this time lag from place of birth to referral center may explain the large number of patients in this study who succumbed prior to any diagnostic or therapeutic intervention

The total salvage rate was 54 per cent This compares favorably with other studies Coleman[6] 42 per cent Varghese and colleagues[2] 43 per cent Fyler and associates[8] 64 per cent If we exclude all infants who died prior to catheterization or surgery the salvage rate is increased to 69 per cent Essentially then earlier referral would result in a much higher survival rate in these patients The surgical survival rate was 71 per cent while 41 per cent of those patients treated medically were alive at the end of 1 year This confirms the opinion of Fyler and colleagues[8] who feel that aggressive management including surgery produces the best results Again the over all surgical results are similar to those y others[9]

Approximately 40 per cent of the surgical procedures were palliative in nature and further surgical intervention in these infants is anticipated in the future A certain number of salvaged infants will probably not survive the second operation It is expected that recent trends towards early total correction using deep hypothermia with cardiac arrest[10] will decrease the necessity for repeated high risk surgery

It is thus seen that early referral accurate diagnosis and aggressive surgical intervention can contribute to salvage of a significantly large group of infants who were only recently thought to be incurable[11] The burden thus falls on the primary physician to recognize the presence of critical congenital heart disease and institute appropriate referral and on the cardiac center to have available on a 24 hour per day basis the facilities for anatomical diagnosis and treatment The need for rapid and safe transportation systems and excellent communication is obvious We feel strongly that no hospital should assume responsibility for care of these infants unless all of the necessary facilities and personnel are available and that the care of these infants requires a complete and total commitment on the part of those assuming this responsibility

Summary

In a retrospective study the incidence of critical congenital heart disease in the State of Wisconsin was determined for the years 1969 1970 Two hundred sixty two infants were identified in 5 pediatric cardiology centers giving an incidence of 1 7 cases per 1 000 live births Patients were admitted to the study on the basis of cardiac catheterization (192) autopsy (53) or surgery without prior catheterization (17)

Lesions most commonly encountered were ventricular septal defects (19 per cent) transposition of the great arteries (13 per cent) patent ductus arteriosus (11 per cent) hypoplastic left heart (10 per cent) and tetralogy of Fallot (9 per cent) Analysis was made to relate the specific cardiac anomaly to the age at which diagnostic and/or therapeutic intervention was required

One hundred nine surgical procedures were performed These included pul

Table V *Number and per cent of deaths in 262 patients*

PATIENTS DEAD = 123 (46 %)		
DEAD BEFORE CATH–	53	(44%)
DEAD DUE TO CATH–	13	(10%)
DEAD – SURGICAL –	32	(26%)
DEAD – MEDICAL –	25	(20%)

Table VI *Surgical results*

PROCEDURE	No PTS	ALIVE	DEAD	SURVIVAL %
Pulmonary Artery Band	31	24	7	77 %
PDA Ligation	24	20	4	83 %
Waterston Shunt	18	8	10	44 %
Resection of Coarctation	8	6	2	75 %
Atrial Septectomy	8	5	3	63 %
Brock Procedure	3	2	1	67 %
Other	17	12	5	70 %
TOTAL	109	77	32	71 %

cedure was chosen for classification Seventy one per cent of the patients (77) survived the surgery The most successful procedures included pulmonary artery banding (77 per cent survived) ligation of a patent ductus arteriosus (83 per cent survived) and resection of coarctation of aorta (75 per cent survived) See Table VI

G *Referral patterns* All patients were identified as to county of residence The center receiving a majority of patients from a particular county received credit as that county s referral area Proximity determined referral area In this sense, each of the 5 centers had its own naturally chosen referral population *Only in counties* equal in distance between 2 or more centers was there a significant division in referral patterns In general, it was both the parents and physicians desire that the infant be cared for closest to home

Discussion

The incidence of critical congenital heart disease comprising 1 7/1 000 live births is somewhat lower than expected (2/1 000) However referrals to neighboring states have not been included and certainly some patients are referred out of state The numbers leaving the state are probably not very significant as the referral patterns previously described, emphasize proximity as one of the most important factors in determining the center chosen for referral Some of the undetected infants are thus dying without referral—probably undiagnosed as having congenital heart disease

Of more concern is the fact that 21 per cent of all patients (53) died before catheterization or surgery could be accomplished and this represented 44 per cent of all deaths—a significant contribution to the total mortality rate The ne [illegible] earlier

Complete right bundle branch block with left axis deviation Significance of vectorcardiographic morphology

Edgar Lichstein M D
Kul D Chadda M D
Prem K Gupta M D
Elmhurst N Y

Complete right bundle branch block with left axis deviation in the frontal plane was noted in 1934 by Wilson Johnston and Barker [1] It was thought that this unusual form of block might in some cases be due to a lesion of one of the sub divisions of the left bundle in addition to right bundle branch block Lenegre[2] and Unger and associates[3] provided pathological support for this interpretation Further confirmation was provided by the experi mental animal studies of Watt and co workers[4] in which sectioning the right bun dle branch after ligating the anterior fibers of the left bundle branch produced the electrocardiographic pattern in question

Studies of vectorcardiographic morphol ogy have attempted to find a relation ship between pattern and clinical course Salzman and colleagues[5] described two basic vectorcardiographic loops which were characterized by the rotation in the hori zontal plane Patients with a Type A or counterclockwise horizontal loop had a better prognosis than patients with a Type B clockwise horizontal loop A similar study by Kulbertus and co workers[6] denied any significant difference between the two groups

This study is concerned with a large group of patients with complete right bun dle branch block and abnormal left axis deviation An attempt is made to correlate the vectorcardiographic morphology and the His bundle electrogram with certain historical features such as dizziness and syncope

Patients and method

The patients in this study included both inpatients and outpatients of a large municipal hospital The majority of pa tients were discovered as a result of screen ing routinely requested ECG s Other pa tients were seen in consultation either be cause of their underlying cardiac disease or for specific evaluation of an abnormal ECG History and physical examination was per formed by the authors at the time the vectorcardiogram (VCG) was recorded Hypertension was thought to be present if repeated blood pressure determinations

F m th Dep rtme t of Med cine D isio of Ca diol gy Mount Si ai Hosp tal Service C ty Ho pital Center t Elmhu t M t S nai School f M d cine of th C ty U er ty f New Y k.
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monary artery banding (31), ligation of a PDA (24) systemic to pulmonary anastamoses (18), resection of aortic coarctation (8) and atrial septectomy (8) Survival rate of all surgical procedures was 71 per cent At the end of 1 year of follow up, 139 patients were alive (54 per cent) However if patients who died without the opportunity for surgery or catheterization are excluded, survival rate was increased to 66 per cent

The authors wish to thank Drs Jay Levy and Marion Ledbetter of Madison Wisc Dr A C V Elston of La Crosse Wisc and Dr George Griese of Marshfield Wisc for their help and cooperation in obtaining data

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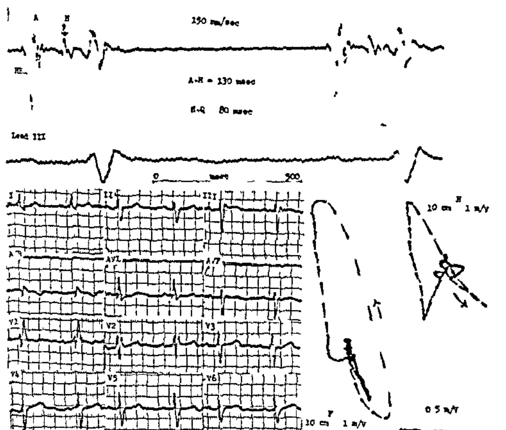


Fig 1 ECG VCG and His bundle electrogram (*HBE*) recorded from a patient in Group A 1 The *initial forces* are directed inferiorly and anteriorly with counterclockwise (CCW) rotation in the horizontal plane The HBE demonstrates delayed conduction distal to the His deflection HBE A = *atrial depolarization* H = His bundle deflection VCG H = horizontal plane F = frontal plane

designated Group A while those with a clockwise loop were designated Group B There were 46 Group A and 19 Group B patients The groups were then subdivided according to the *initial vector in* both the frontal and horizontal plane A summary of significant findings is shown *in Table I*

Group A 1 (Fig 1) Initial forces *interior* and inferior Counterclockwise loop in the horizontal plane *There were 26 patients* in this group 20 men and six women with an average age of 69 years *The most* significant findings were the high incidence of enlarged heart and hypertension (7/26) *and* the high incidence of syncope (12/26) First degree A V block was *noted in four* and transient complete heart block was noted in two Nine of 11 His *bundle re*cordings showed a *prolonged H Q* interval (normal H Q interval 35 to 55 msec) Each of the patients with a prolonged H Q *in*terval had a history of dizziness or syncope

Group A 2 (Fig 2) Initial forces directed superiorly in the frontal plane Counter clockwise horizontal loop with initial force *directed anteriorly* There were 11 patients in this group five men and six women with *an average age of 67* years *Hypertension* was found in four and dizziness or syncope *in five* There were two instances of first degree A V block and one of complete *heart block* Three of six His bundle recordings showed a prolonged H Q interval *and each* of these patients had a history of dizziness or syncope

Group A 3 (Fig 3) Initial forces directed posteriorly and counterclockwise loop *in* the horizontal plane There were nine patients in this group 7 men and 2 women with an average age of *70 years The most*

Table I Summary of significant findings in 65 patients

Group	A1	A2	A3	B1	B2	B3
Average age	69	67	70	74	79	73
Men	20	5	7	6	4	2
Women	6	6	2	4	1	2
Myocardial infarction (clinical)	3	1	8	2	1	1
Angina pectoris	3	1	0	1	0	1
Diabetes mellitus	4	2	1	2	2	1
Hypertension	7	4	2	1	2	1
Enlarged heart (radiographic)	7	3	6	7	3	2
Congestive heart failure	4	3	6	5	3	1
Dizziness/syncope	12	5	2	3	1	0
3° A V block	2	1	0	2	1	0
2° A V block	0	0	1	0	0	0
1° A V block	4	2	2	4	0	0
H Q>55	9	3	6	1	1	0
A H>140	1	1	1	0	0	0
Total His recordings	11	6	7	3	1	0

were greater than 160/90 If the patient was on anti hypertensive medication this information was obtained from the patient s previous record Cardiomegaly was diagnosed radiographically if the cardio thoracic ratio was greater than 0 5 Dizziness and syncope have been grouped together This symptom was recorded as being present only if non cardiac causes could be excluded None of the patients had evidence of acute myocardial infarction There were 44 men and 21 women Their ages ranged between 31 and 93 years with an average age of 70 years

The ECG criteria for inclusion in this study were as follows

1 Total QRS duration of at least 0 12 seconds

2 Mean frontal plane QRS axis of −30 degrees or greater The majority of patients had a small initial R wave in Leads II III and aV_F However this was not required as a criteria Patients with QS complexes in these leads were included thus filling the criteria for left axis and not for left anterior hemiblock

3 Evidence of right bundle branch block manifested by delay and slurring of the R wave in the right precordial leads and slurred S wave in the left precordial leads

VCG s were recorded with the Frank lead system[7] with patients in the supine position and the chest electrodes at the level of the fifth intercostal space Frontal horizontal, and left sagittal loops were recorded in addition to scalar X, Y, and Z The VCG s were recorded on either a DR 12 Electronics for Medicine photographic recorder which displays a dash representing 4 msec or a Hewlett Packard oscilloscopic VCG with loops photographed with a Polaroid camera In the latter instance each dash represented 2 5 msec Conventional reference frames for the horizontal and frontal planes were used for angular measurements

The following information was obtained from each projection of the QRS loop (1) direction of inscription of the QRS loop (2) orientation of the mean QRS forces (3) direction of the initial 20 msec vector and (4) direction and speed of inscription of terminal forces

Twenty eight patients also had a His bundle electrogram which was recorded within one week of the VCG His bundle studies were performed according to the method of Scherlag and associates[8] Paper speeds of 75 and 150 mm per second and a frequency range of 40 to 500 Hz were used

Results

Patients were divided into two groups depending on the direction of rotation of the horizontal loop of the VCG The terminology suggested by Salzman and colleagues[5] was used Patients with a counterclockwise loop in the horizontal plane were

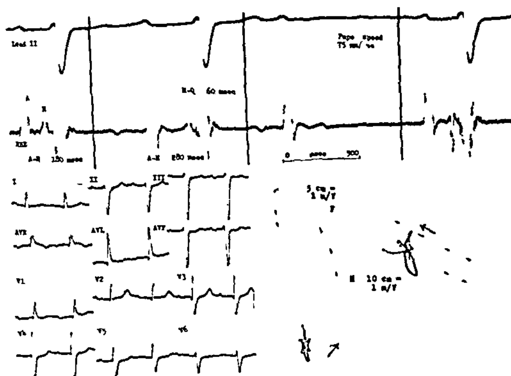


Fig *3* ECG VCG and HBE recorded in a patient in Group A 3 The initial forces are directed inferiorly and posteriorly with a CCW loop in the horizontal plane The HBE shows delay in conduction both proximal and distal to the His deflection (*H*) Mobitz Type I second degree A V block is noted See Fig *1* for explanation of abbreviations

were slightly younger (average age 69 years) than the Group B patients (average age 75 years) The incidence of previous myocardial infarction (Group A 12/46 Group B 4/19) and hypertension (Group A 13/46 Group B 4/19) were similar Diabetes mellitus was slightly more common in Group B (Group A 7/46 Group B 5/19) Cardiomegaly (Group A 16/46 Group B 12/19) and congestive heart failure (Group A 13/46 Group B 9/19) were more common in Group B Episodes of syncope (Group A 19/46 Group B 4/19) and prolonged H Q interval (55 msec or greater) (Group A 19/24 Group B 2/4) were more frequent in Group A patients However in individual cases there was no definite relationship between prolonged H Q interval and syncope

Discussion

The combination of right bundle branch block and abnormal left axis deviation is recognized in approximately 1 per cent of routinely interpreted ECG s[9,10] The most common etiology is coronary artery disease[11,12] Scanlon and colleagues[12] found clinical evidence of coronary artery disease in 41 per cent of a group of patients with this electrocardiographic pattern There is frequently obstruction of the left anterior descending coronary artery since the middle third of the right bundle and the anterior division of the left bundle are supplied by branches of this artery[14]

Diffuse myocardial fibrosis involving the intraventricular conduction pathways is an other etiologic factor described by Lenegre[2] These patients are usually asymptomatic with no history of angina pectoris or valvular disease[1]

A small group of patients with this ECG pattern have calcific aortic stenosis and left ventricular hypertrophy It is thought that the bifascicular block is probably due to a sclerotic degenerative process de

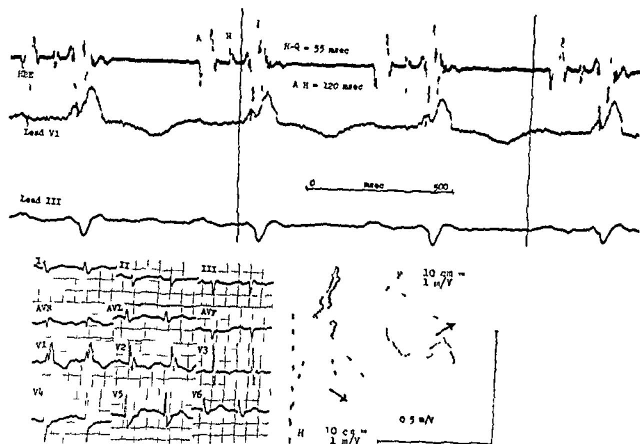


Fig 2 ECG VCG and HBE recorded from a patient in Group A 2 The initial forces are directed superiorly and anteriorly with a CCW loop in the horizontal plane The HBE shows the conduction distal to the His deflection (*H*) to be at the upper limits of normal See Fig *1* for explanation of abbreviations

striking finding in this group was the high incidence of clinical myocardial infarction (8/9) There was also a high incidence of enlarged heart and congestive heart failure (6/9) There were two patients with dizziness or syncope two patients had first degree A V block Six of seven His bundle recordings showed prolongation of the H Q interval but only one of these patients had a history of dizziness

Group B 1 (Fig 4) Initial vectors directed inferiorly anteriorly and to the right Clockwise loop in the horizontal plane There were ten patients in this group six men and four women with an average age of 74 years The most striking findings were the high incidence of an enlarged heart (7/10) and congestive heart failure (5/10) Three patients had dizziness or syncope four had first degree A V block and two had episodes of complete heart block Only one of the three His bundle recordings showed evidence of H Q prolongation This patient did not have a history of dizziness or syncope

Group B 2 (Fig 5) Initial forces directed superiorly in the frontal plane clockwise loop in the horizontal plane There were five patients in this group four men and one woman with an average age of 79 years Three out of five patients had both enlarged heart and congestive heart failure One patient had dizziness or syncope The one His bundle recording performed in this group showed a prolonged H Q interval and was done on a patient with a history of dizziness

Group B 3 (Fig 6) Initial forces directed posteriorly in the horizontal plane with a clockwise rotation There were four patients in this group two men and two women with and average age of 73 years Two of these patients had enlarged heart There were no instances of dizziness or syncope No His bundle electrograms were recorded in this group

Summary of results

A summary of results in the two basic groups is as follows The Group tients

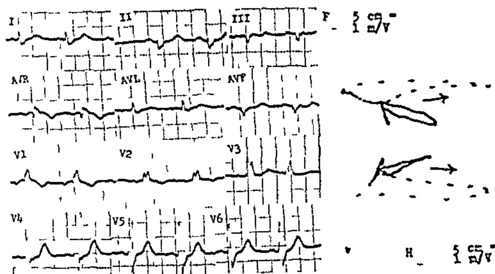


Fig 5 ECG and VCG recorded from a patient in Group B 2 The initial forces are directed superiorly and anteriorly with a CW initial loop in the horizontal plane See Fig 1 for explanation of abbreviations

tions found in order of decreasing frequency were syncope myocardial infarction hypertension diabetes mellitus and angina pectoris A frequent occurrence of hypertension and diabetes mellitus was noted in the series of Scanlon and co workers [13]

Since the VCG morphology varies it was thought that various patterns might have some relationship to the clinical course Salzman and colleagues[5] reported that patients with a clockwise horizontal loop had a higher frequency of overt and symptomatic coronary disease and had a greater frequency of cardiomegaly congestive heart failure and death when compared to patients with a counterclockwise horizontal loop Kulbertus and associates[6] was unable to find any significant clinical difference between two similar groups of patients

Saltzman and colleagues[5] suggested that true posterior wall infarction and fibrosis was an explanation of the anteriorly directed clockwise horizontal loop Hugenholtz and co workers[20] described four out of 33 cases with posterior basal myocardial infarction with a clockwise loop in the horizontal plane Walsh and associates[21] also described occasionally finding clockwise loops in the horizontal plane with posterior wall myocardial infarction

An experimental study by Kulbertus and colleagues[6] showed that an identical clockwise loop in the horizontal plane could be produced in normal controls by stimulation of the posterior surface of the heart A study by Cohen and co workers[22] also showed that this type of pattern may be produced by the introduction of atrial premature beats Both clockwise and counterclockwise loops were produced The presence or absence of underlying heart disease did not appear to affect the type of VCG pattern produced

Several clinical differences were observed in our patients Group A patients were slightly younger than Group B Diabetes mellitus cardiomegaly and congestive heart failure were more common in Group B The amount of cardiomegaly and congestive heart failure in Group B could not be explained by the incidence of hypertension and was thought to be due to more extensive myocardial damage Episodes of syncope and prolonged H Q interval (55 msec or greater) were more frequent in Group A patients However in individual cases there was no definite relationship between prolonged H Q interval and syncope (Table II)

It is concluded that the ECG pattern of right bundle branch block with abnormal left axis deviation represents a wide spectrum of disease and anatomical defects

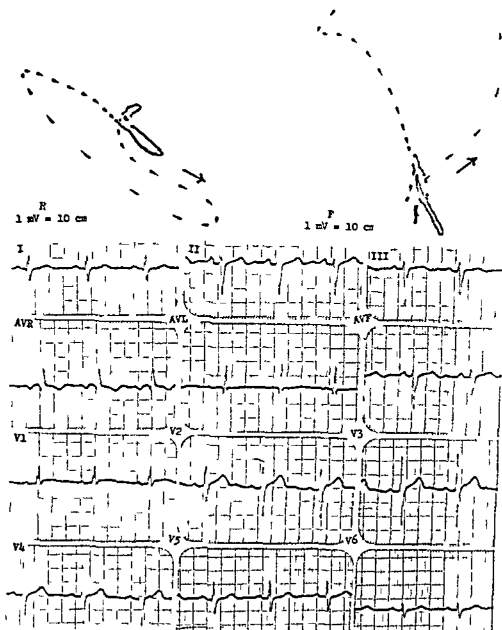


Fig 4 ECG and VCG recorded from a patient in Group B 1 The initial forces are directed inferiorly and anteriorly with a clockwise (CW) loop in the horizontal plane See Fig 1 for explanation of abbreviations

scribed by Lev [15] which extends down from the aorta to involve the membranous septum and the top of the muscular septum

Cardiomyopathy may also produce this pattern as seen in the case described by Castellanos and co workers [16] Autopsy on this patient showed normal coronary arteries but wide spread areas of patchy and diffuse fibrosis This ECG pattern may also be encountered following tricuspid valve replacement[17] and repair of a ventricular septal defect [18]

An important reason for recognizing this pattern is in predicting clinical complication such as complete heart block Lasser Haft and Friedberg[10] report an incidence of 10 per cent while Scanlon Pryor and Blount[13] reported an incidence of 14 per cent In a smaller series reported by Kulbertus and Collignon [19] all 11 patients developed transient or permanent complete heart block and episodes of syncope In 65 patients with this ECG pattern reported by Watt and Pruitt [9] associated clinical condi

Table II Comparison of clinical differences in patients in Groups A and B

No	Age	Group	AH	HQ	A V Conduction	Dizziness/ syncope
1	52	A1	90	50		+
2	83	A1	130	35		
3	84	A1	110	70		+
4	72	A1	270	70	1 AV block	+
5	76	A1	140	80	Intermittent CHF	+
6	90	A1	130	80	1 AV block	+
7	60	A1	80	100	1 AV block	+
8	78	A1	100	90		+
9	81	A1	110	60		+
10	71	A1	90	70	CHB	+
11	87	A1	80	60		+
12	85	A2	120	60		+
13	72	A2	120	45	Intermittent 1 AV block	
14	40	A2	110	50		+
15	77	A2	90	65	CHB	+
16	69	A2	80	45		+
17	78	A2	90	60		+
18	80	A3	100	60		
19	46	A3	110	40		
20	51	A3	110	55		
21	78	A3	170	55	1 AV block and intermittent 2 AV block proximal to His potential	
22	63	A3	90	90		
23	56	A3	90	60		
24	93	A3	AF	70		+
25	70	B1	100	50	Intermittent 1 AV block	+
26	75	B1	120	45		
27	73	B1	80	70		
28	83	B2	90	100	CHB	+

Patient is not on digitalis.

and hypertension (Group A 13/46 Group B 4/19) were similar Diabetes mellitus was slightly more common in Group B (Group A 7/46 Group B 5/19) Cardiomegaly (Group A 16/46 Group B 12/19) and congestive heart failure (Group A 13/46 Group B 9/19) were more common in Group B Episodes of syncope (Group A 19/46 Group B 4/19) and prolonged H Q interval (55 msec or greater) (Group A 19/24 Group B 2/4) were more frequent in Group A patients However in individual cases there was no definite relationship between prolonged H Q interval and syncope

It is concluded that this pattern represents a wide spectrum of disease and anatomical defects The relationship of VCG morphology to clinical course does not appear to be close enough to predict the course of an individual patient or aid in clinical management

The authors wish to thank Richard P Lasser M D for his helpful suggestions in the course of this study

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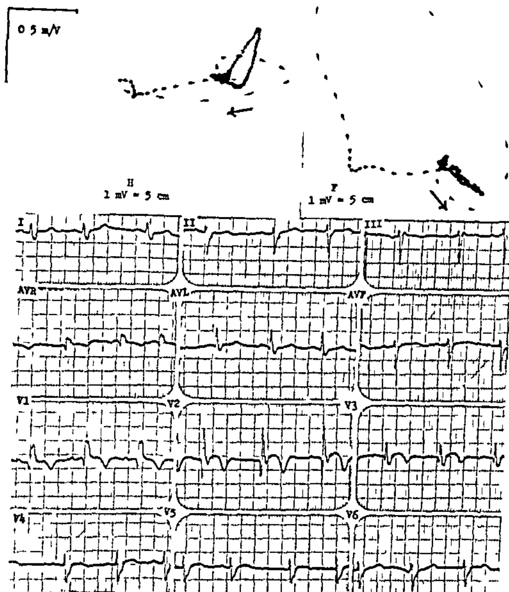


Fig 6 ECG and VCG recorded from a patient in Group B 3 The initial forces are directed inferiorly and posteriorly with a CW loop in the horizontal plane See Fig 1 for explanation of abbreviations

The abnormal initial forces in the frontal plane probably indicate inferior wall myocardial infarction which [23] coupled with the conduction defect suggests disease of both the right and left coronary arteries The abnormal initial forces in the horizontal plane may indicate anterior septal myocardial infarction due to occlusion of the proximal left anterior descending coronary artery or they may be due to the left anterior hemiblock alone [24] The relationship of VCG morphology to clinical course does not appear to be close enough to predict the course of an individual patient or aid in clinical management

Summary

Sixty five patients with a VCG pattern of complete right bundle branch block and left axis deviation (> −30 degrees) were studied There were 46 patients with counterclockwise rotation (Group A) and 19 patients with clockwise rotation (Group B) in the horizontal plane His bundle electrograms were recorded in 24 Group A patients and in four Group B patients

The Group A patients were slightly younger (average age 69 years) than the Group B patients (average age 75 years) The incidence of previous myocardial infarction (Group A 12/46 Gr -4/19)

Left ventricular function in systole and diastole in constrictive pericarditis

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Left ventricular (LV) function may be normal or depressed in constrictive pericarditis Previous studies made in small groups of patients suggest that the mechanical function of the LV is abnormal while there is little information about diastole[1 3]

We have had an opportunity to study a large number of patients with constrictive pericarditis This report will describe the function of the left ventricle in systole and diastole in a consecutive group of 30 patients

Patients

We selected for study 30 consecutive patients with constrictive pericarditis (CP) who were evaluated before operation Patients with atrial fibrillation were excluded as the varying R R interval complicates analysis One patient had atrial flutter with 4 1 atrioventricular block and a regular ventricular response

The clinical electrocardiographic and radiological features of the patients were typical and have been described in detail[4 11] The patients were in cardiac failure and the important clinical features are summarized in Table 1 Twenty seven patients had underlying tuberculous disease one had amoebic infection of the pericardium and in two constriction followed a penetrating stab wound of the chest All the patients were treated with digitalis and diuretics and were fully digitalized at the time of study

The operation of pericardiectomy was made in 18 patients the remainder are presently receiving preoperative anti tuberculous therapy or are being treated conservatively

Methods

Data acquisition Premedication with 10 mg diazepam (Valium) and 50 mg Pethidine was given one hour before study Routine cardiac catheterization was performed through a percutaneous puncture of the right femoral artery and vein or a cutdown in the right antecubital fossa Intravascular and intracardiac pressures were measured through Statham P23 Db bonded strain gauges using the mid-chest level as the zero reference Pulsus paradoxus was measured in the ascending aorta during deep respiration Pressures for calculation were the mean values recorded during several respiratory cycles LV dp/dt was derived from LV pressure using an electronic analog differentiating amplifier without phase lag or distortion

Cardiac output was measured by the

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R cei ed fo p bli ti Aug 28 1972
R pri t req ts t Prof sso M S Got man W tworth Hosp tal P B Jacobs N t l South Africa

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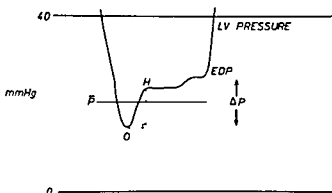


Fig 1 Ventricular diastolic pressure pulse tracing in a patient with constrictive pericarditis *O* is the lowest diastolic pressure and *EDP* is the instant of onset of left ventricular pressure rise *H* is the diastasis plateau and ΔP is the diastolic pulse pressure $\bar{P}$ is the mean diastolic pressure where $\bar{P} = \frac{EDP - O}{2}$ mm Hg

correction made in the measurements The systolic time intervals have two components pre-ejection phase (PEP) from the earliest q or R wave of the ECG to the instant of aortic pressure rise and left ventricular ejection time (LVET) from aortic valve opening to its closure Total electromechanical systole (Q S2) is the time from the onset of ventricular activation on the ECG until aortic valve closure[12 15] The PEP/LVET ratio was also calculated this ratio correlates with the left ventricular ejection fraction[16] PEP and LVET are heart rate dependent we calculated ΔPEP and ΔLVET where the Δ value is the deviation from the normal regression lines of Weissler Harris and Schoenfeld[13] at a given heart rate Our patients were digitalized and it is possible that we should have used the revised regression of Weissler and Schoenfeld[17] allowing for digitalization There is a beat to beat variation of time interval measurements in pulsus paradoxus and we used in our calculations the mean value recorded during several respiratory cycles[12]

Ventricular volumes were measured from the uniplane cineangiogram using the method of Greene and associates[18] and allowing for magnification End-diastolic (EDV) end systolic (ESV) and angiographic stroke index (angio SI) were calculated and were normalized for body surface area The ejection fraction and filling fraction were calculated where

$$\text{Ejection fraction (EF) (\%)} = \frac{EDV - ESV}{EDV} \times 100$$

and

$$\text{Filling fraction (FF) (\%)} = \frac{EDV - ESV}{ESV} \times 100$$

Left ventricular ejection rate was calculated where

$$\text{Ejection rate (ml/sec/M}^2) = \frac{\text{Angio SI (ml/beat/M}^2)}{\text{LVET (msec)}} \times 10^3$$

$\Delta P/\Delta V$ was calculated where ΔP was divided by angiographic *SI* $\Delta V/\Delta P$ is the over all compliance of the ventricle in diastole

The following derived measurements were calculated Circumferential fiber shortening (C_f) where

$$C_f\ (\%) = \frac{C_{dia}\ (cm) - C_{sy}\ (cm)}{C_d\ (cm)} \times 100$$

Mean velocity of circumferential fiber shortening (V_{cf}) where

$$V_{cf}\ (circ/sec) = \frac{C_d\ (cm) - C_{sy}\ (cm)}{C_{dia}\ (cm) \times LVET\ (msec)} \times 10$$

and

C_d = *Inner equatorial LV diameter in diastole*

and

C_s = *Inner equatorial LV diameter in systole*

Table I *Clinical data*

Patient No	*Initials*	*Age (yr)*	*Sex*	*Race*	*Etiology*	*JVP* (cm)*	*Hepato megaly (cm)*	*Edema*	*Ascites*	*Previous pericardial effusion*
1	I M	26	M	W	TB	8	8	+	+	–
2	M W	48	M	B	TB	M	4	–	+	–
3	N N	35	M	B	Trauma	10	8	+	+	±
4	E N	27	M	B	TB	M	5	+	–	+
5	A M	28	F	B	TB	M	12	+	+	–
6	J M	54	M	B	TB	M	6	+	+	–
7	A S	37	M	W	TB	10	3	+	–	Previous pericardiectomy (12 yrs)
8	M N	17	M	B	TB	M	8	–	–	–
9	M N	29	M	B	TB	M	4	+	+	+
10	E N	42	M	B	TB	M	6	+	+	–
11	S N	45	M	B	TB	4	4	+	+	–
12	R E	33	M	W	TB	M	8	+	–	–
13	C M	20	F	B	TB	M	4	+	–	–
14	V N	23	F	B	TB	M	6	+	+	–
15	M M	35	M	B	Amoebiasis	M	5	+	+	+
16	J S	23	M	B	TB	10	3	+	+	+
17	G M	49	M	B	TB	3	7	–	+	–
18	R K	31	M	C	Trauma	6	—	–	–	+
19	S D	50	M	B	TB	8	10	+	+	–
20	M S	30	M	B	TB	M	10	+	–	–
21	M S	55	M	B	TB	8	6	+	+	–
22	J M	50	M	B	TB	M	3	+	+	–
23	A D	48	M	B	TB	5	6	+	–	–
24	B N	28	M	B	TB	M	8	+	+	–
25	M M	14	M	B	TB	10	5	+	+	+
26	K S	27	M	B	TB	8	8	–	–	+
27	S N	27	M	B	TB	6	5	+	+	–
28	S M	44	M	B	TB	M	8	+	+	–
29	J N	43	M	B	TB	M	8	+	+	+
30	G M	46	M	B	TB	M	6	+	+	–

*Abbreviations B = Bantu C = Colored JVP = jugular venous pressure M = jugular venous pressure above angle of mandible in erect position TB = tuberculosis W = white

direct Fick method Routine cardiac catheterization was followed by left ventricular cineangiocardiography in the right anterior oblique (RAO) view using a slow injection of 50 ml of 76 per cent Urografin

Definitions and data analysis The analysis of *diastole* is shown in Fig 1 *O* was the lowest diastolic pressure recorded but we cannot exclude artefact from mechanical overshoot with certainty The *H* point was the instant of pressure inflexion at the end of the rapid filling phase of the left ventricle and was clearly defined in all but three patients who had a rapid heart rate at the time of study and had insufficient time for diastasis End diastolic pressure *(LVEDP)* was the *instant of onset* of the rapid rise of ventricular pressure The mean rate of pressure rise during the rapid filling phase was calculated by dividing the *O H* pressure difference by the *O H* time interval and was expressed in mm Hg per second ΔP was the pressure difference between *O* and *LVEDP* Mean diastolic pressure $(\bar{P})$ was $\frac{LVEDP - O}{2}$ mm Hg

The *time intervals* of the cardiac cycle were measured from the electrocardiogram phonocardiogram and from a simultaneous pressure recording in the ascending aorta The delay time of the catheter manometer system was determined from a comparison of the dicrotic notch of the aortic pressure tracing with the aortic component of the second heart sound and the appropriate

CI (*L/min/M²*)	*SI* (*ml/beat/M²*)	*Angiographic LV volumes* (*ml/M²*)			*SWI* (*Gm M/beat/M²*)	*EF* (%)	C_f (%)	*Mean V* $_f$ (*circ/sec*)	*Mean LV ejection rate* (*ml/sec/M²*)	*PF*	*ΔV/ΔP* (*ml/M²/mm Hg*)	*ΔP/ΔV* (*mm Hg/ml/M²*)
		EDV	*ESV*	*Angio SI*								
3 0	34	97	33	64	53 6	66	—	—	212	1 9[illegible]	3 23	0 31
2 7	33	78	18	60	57 5	77	—	—	229	4 64	5 00	0 20
3 2	53	72	23	43	43 6	68	33	1 66	81	2 18	6 25	0 16
3 0	3[illegible]	71	23	48	36 1	68	34	1 35	190	2 05	4 76	0 21
5 1	46	65	29	36	[illegible]9 9	55	19	0 73	137	1 [illegible]	5 00	0 [illegible]0
3 6	34	63	18	45	41 1	71	4[illegible]	—	—	2 60	—	—
3 2	51	—	—	—	—	—	—	—	—	—	—	—
4 9	6	55	17	38	32 6	69	—	—	—	3 45	—	—
2 8	31	50	20	30	25 3	60	[illegible]5	0 86	104	1 51	2 78	0 36
3 4	34	50	12	38	30 7	[illegible]6	35	1 47	157	3 03	4 [illegible]6	0 [illegible]1
[illegible] 9	39	—	—	—	—	—	—	—	—	—	—	—
2 8	35	—	—	—	—	—	—	—	—	—	—	—
5 5	43	49	14	35	31 6	70	32	1 45	158	2 44	—	—
4 0	35	—	—	—	—	—	—	—	—	—	—	—
3 4	31	—	—	—	—	—	—	—	—	—	—	—
2 1	48	40	20	[illegible]0	23 5	50	25	1 09	94	1 16	2 38	0 42
3 5	38	38	6	3[illegible]	43 5	84	45	1 59	120	8 [illegible]	—	—
4 4	44	35	8	27	31 8	77	—	—	1[illegible]7	6 76	7 69	0 13
[illegible] 3	27	—	—	—	—	—	—	—	—	—	—	—
[illegible] 6	6	—	—	—	—	—	—	—	—	—	—	—
4 0	45	34	13	21	19 2	62	25	1 00	84	1 62	2 33	0 43
2 3	23	—	—	—	—	—	—	—	—	—	—	—
2 2	36	30	12	18	20 2	60	27	1 29	93	1 [illegible]8	[illegible] 04	0 49
1 6	18	—	—	—	—	—	—	—	—	—	—	—
4 4	38	23	10	13	12 7	57	9	—	247	1 60	1 39	0 7[illegible]
2 2	2[illegible]	23	6	17	16 5	73	29	0 41	60	2 57	1 47	0 68
2 7	23	19	5	14	13 6	73	18	1 44	55	3 04	2 04	0 49
2 2	27	19	4	15	12 8	78	28	0 71	49	3 45	1 61	0 6
1 3	13	—	—	—	—	—	—	—	—	—	—	—
2 4	8	15	4	11	8 6	72	25	0 90	40	2 78	1 59	0 63
3 1	35	46	14	32	29 2	68	28	1 18	124	2 90	3 40	0 39
1 0	11	23	9	16	13 8	9	9	0 4[illegible]	63	1 80	1 93	0 [illegible]0
3 5 ± 0 7 39	46 ± 8 39	70 ± 20 40	24 ± 10 40	45 ± 12 40	66 ± 18 41	67 ± 8 40	26 ± 4 3		159 ± 31 42			

CI = ca d c d DPR = ate f p ssu rise i e rly d stol EDV = e d d stol c v lum ESV = e d y t l vol me EF = ject o
LV j t n t = left t ic la ject n r te MAP = m rterial pre sur $\bar{P}$ = m a d tol p essure ΔP = dia tol c pre sure
RVEDP = right ventricular nd-d a t l pressure SI = st ok ind SWI = str ke work index ΔV = v lum cha g in diastole V =

grams free of ectopic beats in our calculations Measurements of left ventricular volume and particularly end systolic volume are less reliable when the ventricle is small in these circumstances the ventricle is irregular and muscle trabeculae and papillary muscles encroach on the cavity This magnifies errors in calculation of the systolic volumes

Venous filling pressure was altered clinically by the vigor and duration of diuretic therapy and could be reduced by prolonged inpatient treatment This may account for the variability in end-diastolic pressures when they were related to the severity of the disorder as assessed by other criteria

Results

The measured and derived hemodynamic and angiographic measurements are given in Table II

Disability Shortness of breath was not a

Table II Hemodynamic and angiographic measurements

Patient No	Pressures (mm Hg)										Mean DPR (mm Hg/sec)	Peak LV dp/dt (mm Hg/sec)	AV O_2 diff (ml/L)
	MAP*	Pulsus paradoxus	Mean RA	RVEDP	Mean PAP	Mean PCWP	LV O point	LVEDP	$\bar{P}$	ΔP			
1	92	5	25	28	36	28	10	30	20	20	188	1 117	40
2	94	12	26	26	35	28	20	33	27	13	90	1 480	44
3	80	—	14	14	19	11	8	16	12	8	55	1 150	37
4	86	13	23	22	33	23	22	32	27	10	57	—	41
5	82	14	18	20	28	21	16	23	20	7	138	—	23
6	96	30	26	28	31	26	—	—	—	—	—	—	33
7	88	12	22	28	33	26	8	20	17	6	80	1 060	37
8	88	12	23	30	36	26	—	—	—	—	—	—	27
9	104	16	6	6	20	8	4	15	10	11	58	—	42
10	80	20	18	20	40	17	12	20	16	8	63	—	35
11	90	10	7	10	20	—	8	13	11	5	27	906	41
12	75	—	22	25	33	25	9	24	17	15	144	1 050	40
13	95	24	19	18	28	26	—	—	—	—	13	2 114	23
14	93	14	21	22	27	21	15	26	21	11	151	1 288	31
15	92	20	8	15	17	9	7	17	12	10	86	—	34
16	105	28	23	30	35	27	18	27	23	9	63	—	60
17	100	15	1	3	10	4	—	—	—	—	—	—	34
18	93	10	11	12	20	12	10	14	12	4	60	1 208	27
19	85	10	21	22	30	20	12	19	16	7	50	—	43
20	105	55	19	19	34	25	12	25	19	13	144	—	44
21	87	10	8	8	19	16	7	16	12	9	40	—	29
22	80	20	18	20	26	7	8	19	14	11	69	1 270	38
23	100	24	18	20	25	19	14	24	19	10	143	1 428	55
24	75	15	22	20	30	25	25	35	30	10	167	—	60
25	87	31	17	20	30	21	11	21	16	10	125	—	3[illegible]
26	110	35	20	20	30	20	19	30	25	11	100	—	54
27	90	25	16	20	20	15	15	22	19	7	50	—	45
28	90	20	18	23	22	22	15	24	20	9	67	—	4[illegible]
29	105	60	24	30	33	30	14	28	21	14	214	—	8[illegible]
30	85	18	27	21	33	28	20	27	24	7	60	—	5[illegible]
Mean	91	21	18	20	28	20	13	23	18	10	93	1 314	41
±SD	9	13	7	7	7	7	5	7	5	3	52	337	13
Normal value	90 ± 15	—	3 ± 2	4 ± 3	14 ± 5	9 ± 4	3 ± 2	9 ± 4	6 ± 3	6 ± 3	—	1 600 ± 400	41 ±
Ref	37	—	37	37	37	37	38	37	38	38	—	38	39

*Abbreviations Angio SI = angiographic stroke index AV O_2 Diff = arterio venous oxygen difference Cf = circumferential fiber shorteni fraction FF = filling fraction LV dp/dt = 1st derivative of left ventricular pressure LVEDP = left ventricular end diastolic pres change (LVEDP O) PCWP = pulmonary capillary wedge pressure PAP = pulmonary artery pressure RA = right atrial press velocity of circumferential fiber shortening

Pericardial thickening obscured the outline of the left ventricle and true LV wall thickness and mid wall circumference could not be measured

The LV stroke work index (SWI) was calculated where

LV SWI (Gm M /beat/M²) =
Angio SI (ml /beat/M²) ×
(MAP LVEDP) (mm Hg) × *0 0136*

Statistical analysis The results were analyzed using a Wang 700 programmable calculator and standard statistical methods

Critique of methods Respiratory gymnastics and the subsequent delivery of a large volume of contrast medium during angiography disturbs the steady state of the circulation [19] Angiographic volumes are used as a standard of reference for measurement of ventricular volumes but we are hesitant to accept this without reservation We used only technically perfect angio

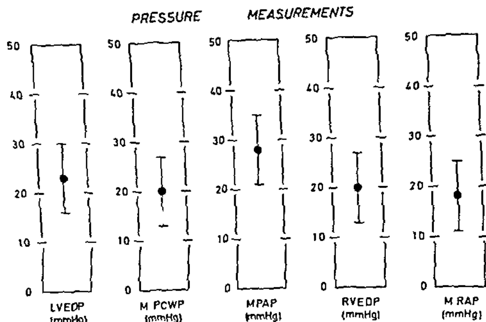


Fig 3 Pressure measurements in constrictive pericarditis The ventricular end-diastolic pressures were elevated and were 2 to 3 mm Hg higher than the corresponding atrial pressures Left heart pressures were 2 to 3 mm Hg higher than the corresponding right heart pressures Mean pulmonary artery pressure (*MPAP*) was slightly elevated (28 ± 7 mm Hg) Mean values ± 1 SD are shown

striction and very small volumes had a reduced LV ejection rate (LVER) there was a significant linear correlation between LVER and EDV

The linear relationship between EDV and angio SI was a reflection of a fairly constant *ejection fraction* (68 ± 9 per cent) which was maintained even at a low EDV This relationship is shown in the upper panel of Fig 6

Circumferential fiber shortening (C_f) and *mean velocity of circumferential fiber shortening* (V_{cf}) were normal or slightly reduced (C_f = 28 ± 9 per cent V_{cf} = 1 18 ± 0 42 circ/sec) (Fig 7) This was expected as they measure relative fiber shortening and correct for the reduced EDV the measurements were related to ejection fraction and left ventricular ejection time which were within the range of normal

Stroke work Left ventricular stroke work index was reduced (mean LVSWI = 29 2 ± 13 8 Gm M /beat/M ²) it correlated with the severity of constriction as assessed by a reduction in EDV ($P < 0\,001$) (Fig 8) Mean arterial pressure was normal and LVEDP was elevated but the fall in SWI reflected the decrease in SI

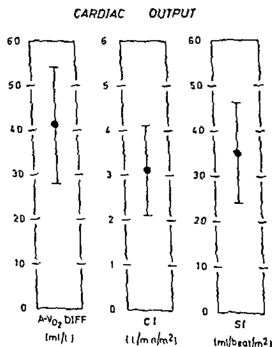


Fig 4 Measurements of mean arteriovenous oxygen difference (*A VO diff*) cardiac index (*CI*) and stroke index (*SI*) were normal but patients with severe constriction had a wide A V O_2 difference and a low cardiac and stroke index Mean values ± 1 SD are shown

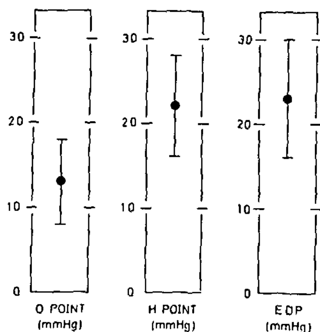


Fig 2 Left ventricular diastolic pressures in constrictive pericarditis (CP) The pressures were elevated with a dip and plateau configuration Mean values ± 1 SD are shown

prominent feature, however all the patients had a high venous filling pressure with severe systemic congestion and fluid retention even though their disability grading was mild or moderate Some patients were not severely disabled after prolonged bedrest and intensive diuretic therapy It is not always possible in constrictive pericarditis to correlate abnormalities of ventricular function with shortness of breath

Pressure measurements Figs 2 and 3 summarize the pressure measurements in patients with CP *Left ventricular O H and EDP* were 13 ± 5 mm Hg 22 ± 6 mm Hg, and 23 ± 7 mm Hg They were elevated and abnormal and 2 to 3 mm higher than the corresponding pressures in the *right ventricle* (RVEDP = 20 ± 7 mm Hg) The left atrium and pulmonary vein were entered retrogradely in several patients the two pressures were identical and were equal to the pulmonary capillary wedge pressure (PCWP) recorded at the same time and there was no evidence of constriction of the orifices of the pulmonary veins or of annular constriction of the mitral valve *Mean PCWP* (20 ± 7 mm Hg) and *mean right atrial (RA) pressure* (18 ± 7 mm Hg) were identical to the corresponding pressure pulse contours in the two ventricles in diastole, but it is noteworthy that the mean atrial pressure was lower than the ventricular EDP This reflects the importance of atrial systole in filling the ventricle and raising the EDP

The *mean pulmonary artery pressure* (MPAP) was 28 ± 7 mm Hg and was only slightly elevated despite the elevation of LVEDP and PCWP The absence of important pulmonary arterial hypertension contrasts these patients with those who have LV failure from coronary artery disease or congestive cardiomyopathy and in whom severe pulmonary hypertension accompanies a similar elevation of LVEDP

The cardiac output The mean *arteriovenous oxygen difference* (A V O_2 diff) was normal but there was a large scatter in individual patients (41 ± 13 ml /L) and several patients had a wide difference Mean *cardiac index* (CI) and *stroke index* (SI) were at the lower limit of normal (CI = 3 1 ± 1 0 L /min /M ² SI = 35 ± 11 ml / beat/M ²) in patients with severe constriction they were low (Fig 4)

LV dp/dt Peak LV dp/dt was normal or slightly reduced (1,314 ± 337 mm Hg/sec)

Angiographic volume measurements Left ventricular end diastolic (EDV) end systolic (ESV), and stroke volumes were reduced (EDV = 46 ± 22 ml /M ² ESV = 14 ± 9 ml /M ² and angio SI = 32 ± 16 ml /M ²) (Fig 5) These volumes reflected the degree of constriction and the patients could be divided into three groups on arbitrary criteria severe (EDV < 25 ml /M ²) moderate (EDV 25 to 50 ml / M ²), and mild (EDV > 50 ml /M ²)

A significant linear relationship between EDV and angiographic SI is shown in Fig 6 Patients with severe constriction and a very small EDV had a corresponding decrease in stroke index (SI = 0 68 EDV + 0 86 ± 4 50 r = +0 96 p < 0 001) The fall in EDV and SI seem to be the most reliable indices of the severity of constriction Patients with more severe constriction in general had a larger pulsus paradoxus pulsus paradoxus was difficult to interpret since it depended on the amount of intrathoracic pressure change

The mean *left ventricular ejection rate* was at the lower limit of normal (124 ± 63 ml /sec /M ²) but patients with severe con

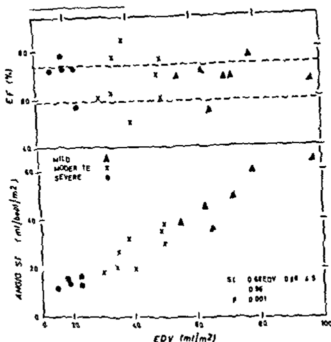


Fig 6 Linear relationship between end-diastolic volume (*EDV*) and angiographic stroke index (*SI*). The patients were divided into three arbitrary groups on the basis of their EDV: mild (EDV > 50 ml/M²), moderate (25 to 50 ml/M²) and severe (EDV < 25 ml/M²). Patients with severe disease had a low EDV and a low SI. Ejection fraction (*EF*) was within the range of normal (dotted lines, *upper panel*)

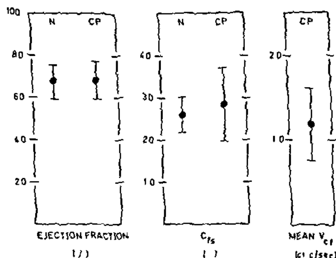


Fig 7 Angiographic measurements of fractional fiber shortening in normal subjects (*N*) and in patients with constrictive pericarditis (*CP*). Ejection fraction, circumferential fiber shortening (C_{fs}) were normal in CP. Mean velocity of circumferential fiber shortening (V_{cf}) was slightly reduced

($\bar{P}$) did not differentiate between mild and severe constriction

The relationship between the rate of pressure rise in early diastole and the LVEDP is shown in Fig 16. The rate of diastolic pressure rise was a function of the absolute ventricular pressure but was not related to EDV and the degree of constriction

Filling fraction was normal, thus mea

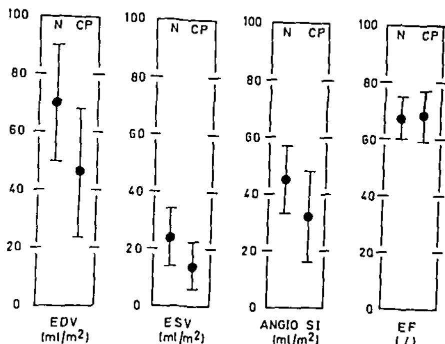


Fig 5 Angiographic left ventricular volume measurements in constrictive pericarditis (*CP*) and in normal subjects (*N*) [40] End diastolic end systolic and stroke volumes were reduced in CP but ejection fraction (*EF*) was normal

Systolic time intervals PEP LVET, and Q S_2 were normal or marginally prolonged (Table III) and the relationships to heart rate are shown in Figs 9, 10, and 11 The figures show the regression of Weissler, Harris and Schoenfeld[13] for normal subjects and of Weissler and Schoenfeld[17] for normal digitalized subjects The negative correlation between PEP and LV dp/dt is shown in Fig 12 There was no significant correlative relationship between LVET and SI but patients with a small stroke index always had a shortened LVET The values of PEP/LVET clustered around the normal regression of Garrard Weissler and Dodge[16] since ejection fraction was normal

Left ventricular compliance The *LV diastolic pressure pulse* showed an early diastolic dip (O point) a rapid filling wave ending at the H point a significant plateau in diastasis and an important a wave A detailed analysis of the diastolic pressures and the relationship to end diastolic volume (EDV) is shown in Fig 13 This shows that patients with severe constriction (EDV less than 25 ml /M²) had high diastolic pressures and a small diastolic pulse pressure (ΔP) Patients with mild constriction (EDV >50 ml /M²) also had high end diastolic pressures but a wider diastolic pulse pressure (ΔP) Paradoxically patients with moderately severe constriction had less elevation of the diastolic pressures ΔP was intermediate between the two groups The reason for this discrepancy is not clear We suggest that patients with moderate and severe constriction received more vigorous therapy than patients in the mild group only patients with moderate disease were able to respond and reduce their blood volume and diastolic pressures

The *compliance* (distensibility index) of the left ventriculopericardial system (ΔV/ΔP) was reduced and was related to EDV in a linear fashion (Fig 14) Patients with severe constriction had a small EDV and a low compliance [20]

Fig 15 shows the relationship between ΔP/ΔV and $\overline{P}$ to show the passive elastic modulus of the ventriculo pericardial system measured according to the method of Diamond and Forrester and co workers [21,22] Patients with severe disease had a low compliance and a high passive elastic

$$\text{modulus } \frac{(\Delta P/\Delta V)}{\overline{P}} \quad \text{Mean diastolic pressure}$$

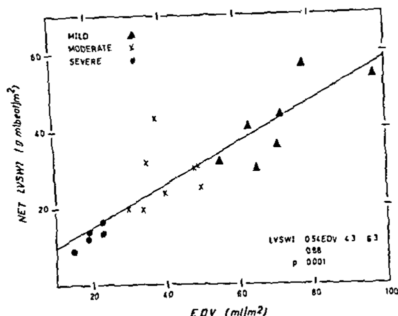


Fig 8 Linear relationship between net left ventricular stroke work index (LVSWI) and LV end-diastolic volume (EDV) Patients with severe constriction and a small EDV had a low net LVSWI

by pericardiectomy [2 11 23] Ventricular filling pressures fall and cardiac output improves but they do not return to normal in the immediate postoperative period The high venous filling pressure persists for 2 to 3 weeks and returns to normal in 2 to 3 months Harrison Crawford and Lau[2] made similar sequential studies of left ventricular function in a patient studied 7 weeks and 13 months after operation

There are few reports which describe measurements of the mechanical function of the ventricle Stroke output is limited and this has been attributed to a myocardial factor Harvey and associates [1] in 2 patients decreased RV filling pressure by treatment with digitalis and diuretics—cardiac output increased in one and decreased in the other the change was equated with an improvement in myocardial performance [1] A simultaneous fall in blood volume occurred and is a more likely cause for the fall in pressure This change is in keeping with our own clinical experience digitalis and diuretic therapy produces a small but significant decrease in venous pressure hepatic enlargement and edema a non specific consequence of a moderate decrease in blood volume

Vogel and colleagues[3] studied ventricular dynamics and showed a significant reduction in EDV ESV SI, EF C_f and V_{cf} Their normal range of values for EF is high but comparative figures are valid and their data suggest that muscle fibers are compressed and that shortening is diminished in severe constriction

Albers Hugenholtz and Nadas[21] studied two patients with CP and atrial septal defect (ASD) The ejection fraction in one patient was 37 per cent before operation and returned to normal after pericardiectomy The return to normal excludes an important myocardial factor and we believe that the ASD acted as a vent for the left atrium decompressed the heart into the systemic circulation and permitted more severe constriction

Dines Edwards and Burchell[20] studied 11 necropsy cases of CP and showed myocardial atrophy with a uniform decrease in diameter of myocardial fibers Atrophy was not confined to the epicardial region adjacent to the constricting material In CP intraventricular pressure and wall thickness are normal but cavity size is diminished systolic wall stress is low stroke output and stroke work are decreased and these factors may be responsible for disuse muscle fiber atrophy analogous

Table III *Time interval measurements*

Patient No	*PEP*	*ΔPEP*	*ΔPEP$_{d\ g}$*	*LVET*	*ΔLVET*	*ΔLVET$_{d\ g}$*	*Q-S$_2$*	*ΔQ-S$_2$*	*ΔQ-S$_{2d\ g}$*	*HR*	*PEP/LVET*
1	150	+53 0	+68 0	300	+31 5	+46 5	450	+82 5	+11? 5	85	0 50
2	90	−7 8	+7 2	280	+8 1	+23 1	370	−1 7	+28 3	83	0 32
3	120	+22 2	+37 2	200	−71 9	−56 9	320	−51 7	−21 7	83	0 60
4	90	−3 4	+11 6	250	−3 2	+11 8	340	−8 6	+21 4	94	0 36
5	90	+9 0	+24 0	260	+50 0	+65 0	350	+61 0	+91 0	130	0 35
6	80	−9 8	+5 2	210	−27 9	−12 9	290	−39 7	−9 7	103	0 38
7	80	−25 8	−10 8	250	−25 9	−10 9	360	−53 7	−23 7	63	0 29
8	110	+12 2	+27 2	260	−11 9	+3 1	370	−1 7	+28 3	83	0 4?
9	70	−25 8	−10 8	290	+26 6	+41 6	360	−1 2	+28 8	88	0 ?4
10	90	+1 8	+16 8	240	+8 9	+23 9	330	+8 7	+38 7	107	0 38
11	—	—	—	—	—	—	—	—	—	—	—
12	70	−29 4	−14 4	260	−18 7	−3 7	330	−50 1	−20 1	79	0 27
13	50	−31 0	−16 0	220	+10 0	+25 0	270	−19 0	+11 0	130	0 23
14	83	−7 2	+7 8	250	+3 2	+18 2	333	−2 0	+28 0	107	0 33
15	120	+?9 0	+44 0	240	−3 0	+12 0	360	+24 0	+54 0	100	0 50
16	140	+46 6	+61 6	230	−23 2	−8 2	370	+21 4	+51 4	94	0 61
17	110	+12 2	+27 2	280	+8 1	+23 1	390	+18 3	+48 3	83	0 39
18	90	−1 0	+14 0	240	−3 0	+12 0	330	−6 0	+24 0	100	0 31
19	70	−19 8	−4 8	260	+22 1	+37 1	330	+0 3	+30 3	103	0 27
20	80	−14 6	+0 4	260	+1 7	+16 7	340	−14 9	+15 1	91	0 31
21	130	+34 2	+49 2	250	−13 4	+1 6	380	+18 8	+48 8	88	0 52
22	80	−21 8	−6 8	?90	+1 1	+16 1	370	−2? 7	+7 3	73	0 ?8
23	90	+9 0	+24 0	210	+9 5	+24 5	300	+16 5	+46 5	125	0 43
24	140	+45 4	+60 4	240	−18 3	−3 3	380	+25 1	+55 1	91	0 58
25	70	−13 0	+2 0	230	+21 0	+36 0	300	+6 0	+36 0	120	0 30
?6	90	+5 0	+?0 0	200	−17 5	−2 5	290	−14 5	+15 5	115	0 45
27	120	+25 4	+40 4	260	+1 7	+16 7	380	+25 1	+55 1	91	0 46
28	110	+4 2	+19 2	300	−5 9	+9 1	410	−3 7	+26 3	63	0 37
29	120	+31 8	+46 8	210	−21 1	−6 1	330	+8 7	+38 7	107	0 57
30	50	−44 6	−29 6	280	+21 7	+36 7	330	−?4 9	+5 1	91	0 18
Mean	95	+3 0	+18 0	?51	−1 4	+13 6	347	+0 0	+30 0	96	0 39
± SD	25	25 4	25 4	29	23 1	23 1	39	30 3	30 3	18	0 12
Normal value		0 ± 12	0 ± 12		0 ± 10	0 ± 10		0 ± 14	0 ± 14		0 35 ± 0 04

*Abbreviations HR = heart rate (beats/min) LVET = left ventricular ejection time (msec) PEP = pre ejection phase (msec) Δ value = deviation from normal when corrected for heart rate[13] Δ value$_{d\ g}$ = deviation from normal when corrected for heart rate and digitalization[17]

surement was related to ejection fraction $(EF \approx \frac{1}{1 - EF} - 1)$ the calculation magnified small errors in systolic measurements

Discussion

Review of the literature There are several excellent reviews of the aberrations of pressure and flow in constrictive pericarditis[1, 2, 10, 11, 23, 27] Cardiac and stroke output are low at rest and cannot increase normally on exercise, ventricular diastolic pressures are elevated with a dip and plateau configuration and the two ventricular diastolic pressure pulse contours are very similar Important pulmonary hypertension does not occur and this may be due to the inability of the right ventricle to increase its output on exercise

Kesteloot and Denef[25] described a syndrome of severe constriction of rapid onset and short duration associated with a high early diastolic ventricular pressure loss of the y descent and a hemodynamic pattern resembling myocardial fibrosis[25] These patients have severe constriction and correspond to our patients with an EDV of less than 25 ml/M^2 and a narrow diastolic pressure pulse measurement of ventricular volumes clearly distinguishes these patients from those with primary myocardial disease

The hemodynamic pattern is modified

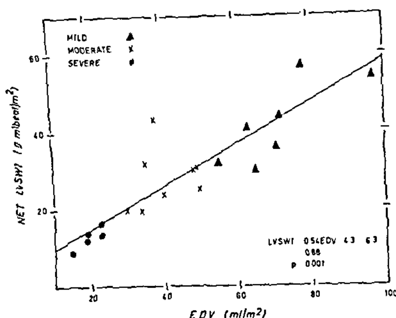


Fig. 8 Linear relationship between net left ventricular stroke work index (*LVSWI*) and LV end-diastolic volume (*EDV*). Patients with severe constriction and a small EDV had a low net LVSWI

by pericardiectomy [2,11,28] Ventricular filling pressures fall and cardiac output improves but they do not return to normal in the immediate postoperative period The high venous filling pressure persists for 2 to 3 weeks and returns to normal in 2 to 3 months Harrison Crawford and Lau[2] made similar sequential studies of left ventricular function in a patient studied 7 weeks and 13 months after operation

There are few reports which describe measurements of the mechanical function of the ventricle Stroke output is limited and this has been attributed to a myocardial factor Harvey and associates [1] in 2 patients decreased RV filling pressure by treatment with digitalis and diuretics—cardiac output increased in one and decreased in the other the change was equated with an improvement in myocardial performance [1] A simultaneous fall in blood volume occurred and is a more likely cause for the fall in pressure This change is in keeping with our own clinical experience digitalis and diuretic therapy produces a small but significant decrease in venous pressure hepatic enlargement and edema a non specific consequence of a moderate decrease in blood volume

Vogel and colleagues[3] studied ventricular dynamics and showed a significant reduction in EDV ESV SI, EF C_f and V_{cf} Their normal range of values for EF is high but comparative figures are valid and their data suggest that muscle fibers are compressed and that shortening is diminished in severe constriction

Albers Hugenholtz and Nadas[29] studied two patients with CP and atrial septal defect (ASD) The ejection fraction in one patient was 37 per cent before operation and returned to normal after pericardiectomy The return to normal excludes an important myocardial factor and we believe that the ASD acted as a vent for the left atrium decompressed the heart into the systemic circulation and permitted more severe constriction

Dines Edwards and Burchell[30] studied 11 necropsy cases of CP and showed myocardial atrophy with a uniform decrease in diameter of myocardial fibers Atrophy was not confined to the epicardial region adjacent to the constricting material In CP intraventricular pressure and wall thickness are normal but cavity size is diminished systolic wall stress is low stroke output and stroke work are decreased and these factors may be responsible for disuse muscle fiber atrophy analogous

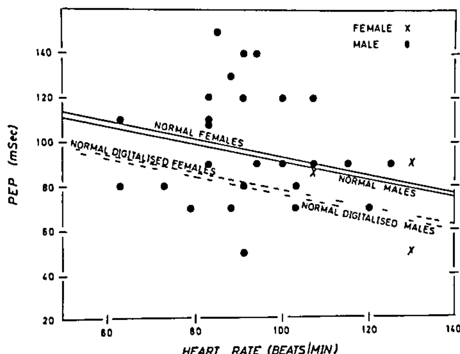


Fig 9 Relationship between pre ejection phase (*PEP*) and heart rate (HR) in patients with constrictive pericarditis The regression lines of Weissler Harris and Schoenfeld[18] for normal undigitalized subjects and of Weissler and Schoenfeld[17] for normal digitalized subjects are shown PEP was normal or slightly prolonged in CP

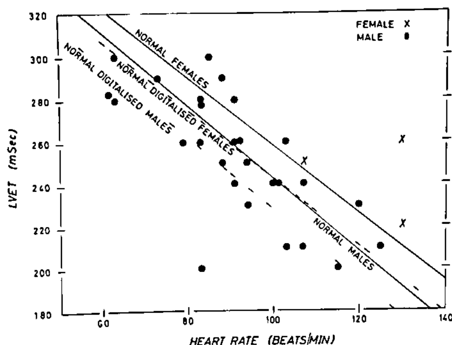


Fig 10 Relationship between left ventricular ejection time (*LVET*) and heart rate (HR) Regressions are shown for normal digitalized and undigitalized subjects[18,17] LVET was normal or slightly reduced in CP

to skeletal muscle atrophy following immobilization of a limb[21] This may account for the delayed return of the hemodynamics to normal following pericardiectomy when ventricular volumes, wall stress and stroke work are returned to normal Dines and colleagues[10] selected a specific group of patients whose constriction was so severe that they died and were studied at autopsy

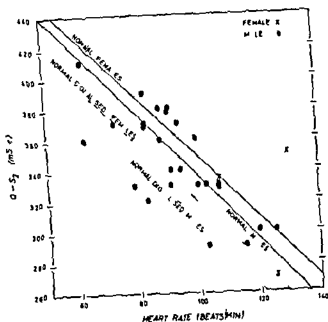


Fig *11* Relationship between Q S_2 and heart rate (HR) Q-S_2 was normal in CP

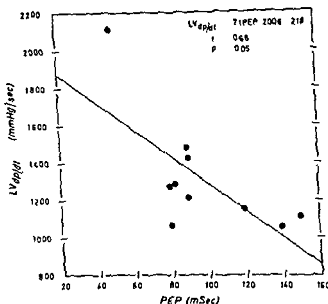


Fig *12* Relationship between pre-ejection phase (*PEP*) and peak *LV dp/dt* in patients with constrictive pericarditis Peak LV dp/dt was slightly reduced in some patients and this was reflected in PEP

Present study

SYSTOLIC FUNCTION The end-diastolic end systolic and stroke *volumes* of the left ventricle reflected the degree of constriction *patients with* severe disease had small volumes Patients *with* severe constriction and a low EDV had a low stroke index stroke work index and left ventricular *ejection rate*

Ejection fraction was normal In health and disease *the* ejection fraction is a sensitive index of *ventricular* dysfunction [22,23] Our results show that absolute fiber shortening *is reduced and* related to end diastolic

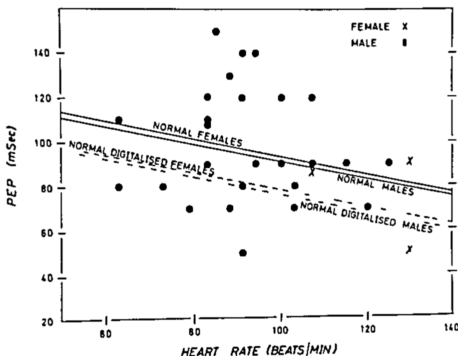


Fig 9 Relationship between pre ejection phase (*PEP*) and heart rate (HR) in patients with constrictive pericarditis The regression lines of Weissler Harris and Schoenfeld[16] for normal undigitalized subjects and of Weissler and Schoenfeld[17] for normal digitalized subjects are shown PEP was normal or slightly prolonged in CP

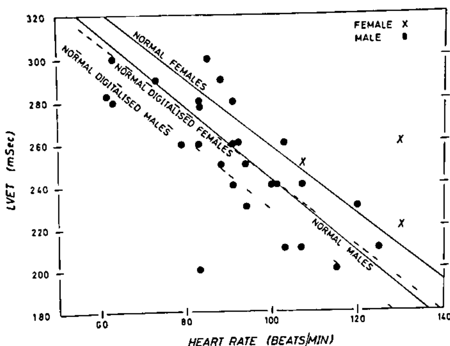


Fig 10 Relationship between left ventricular ejection time (*LVET*) and heart rate (HR) Regressions are shown for normal digitalized and undigitalized subjects[16,17] LVET was normal or slightly reduced in CP

to skeletal muscle atrophy following immobilization of a limb[31] This may account for the delayed return of the hemodynamics to normal following pericardiectomy when ventricular volumes, wall stress and stroke work are returned to normal Dines and colleagues[10] selected a specific group of patients whose constriction was so severe that they died and were studied at autopsy

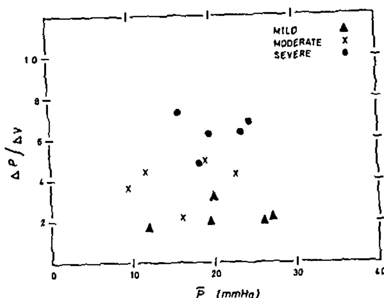


Fig *15* Relationship between $\Delta P/\Delta V$ and mean diastolic pressure ($\bar{P}$) The passive elastic modulus (i e the coefficient a in y = ax + b) was elevated in constrictive pericarditis and was higher in patients with more severe disease as assessed by quantitative angiography

acts as a parallel restricting or inertial element and may impede shortening Additional work is then needed to shorten the inner layers of the constricting material or to overcome myocardial viscosity

We have not assessed *contractility* in detail but *peak LV dp/dt* is normal or slightly reduced

SYSTOLIC TIME INTERVALS The systolic time interval measurements reflected the hemodynamic status PEP correlated with LV dp/dt while LVET was slightly reduced in patients with severe constriction and a diminished stroke index the PEP/LVET ratio reflected the ejection fraction and was normal in most patients Similarly the mean values for ΔPEP ΔLVET and $\Delta Q\,S_2$ were normal

The systolic time intervals are valuable in the differential diagnosis of patients with cardiac failure without murmurs in primary myocardial disease these measurements are invariably abnormal [12,15]

DIASTOLIC FUNCTION There are no human studies of the diastolic compliance of the ventriculo pericardial system in constrictive pericarditis [21,24,26] The overall *compliance* (C_T) can be resolved into two elements in parallel the compliance of the pericardium (C_P) and the compliance of the myocardium (C_M) where

$$\frac{1}{C_T} = \frac{1}{C_P} + \frac{1}{C_M}$$

It is likely that the compliance of the abnormally thickened pericardium overshadows that of the ventricle in constrictive pericarditis

We have expressed *compliance* in two different ways as compliance (or distensibility index) and as the passive elastic modulus [21,22] We have shown a linear relationship between compliance ($\Delta V/\Delta P$) and end-diastolic volume This relationship can be expres ed in the form $\frac{dV}{dP} = kV$ assuming that $\Delta V = dV$ and $\Delta P = dP$ over a wide range of values since we did not make simultaneous instantaneous measurements of ventricular pressure and volume This means that patients with a small tightly constricted ventricle had a low compliance of the ventriculo pericardial system but that the specific compliance $\frac{(\Delta V/\Delta P)}{EDV}$ was constant for constrictive pericarditis ($\Delta V/\Delta P$ = 0 04 EDV + 1 42 ± 1 54)

The method of Diamond and Forrester[21] was used to calculate the *passive elastic modulus* which is the coefficient of $\bar{P}$ in the relationship

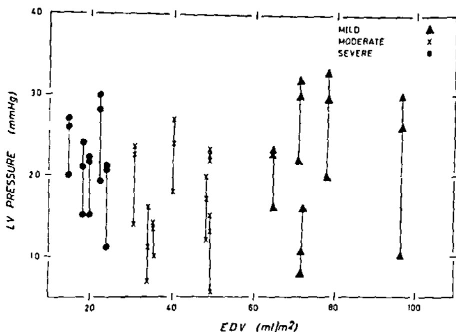


Fig *13* Relationship between LV end diastolic volume (*EDV*) and the diastolic *LV pressures* The O point H point and EDP are shown for each patient and the values in each patient are joined by a vertical line The EDP was similar in all the patients but patients with mild disease had wide diastolic pulse pressures (ΔP) This was small in patients with severe constriction and a small EDV

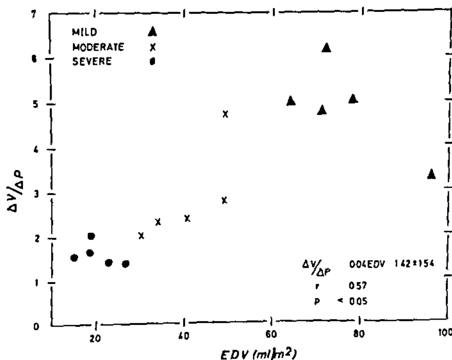


Fig *14* Simple linear relationship between LV distensibility index (*ΔV/ΔP*) and LV end diastolic volume (*EDV*) Patients with severe disease had a small EDV and a low distensibility index

length, but fractional shortening is normal in patients in whom the ventricle is extrinsically splinted so that the crenated compressed fibers operate at a mechanical disadvantage The fibers cannot be stretched to a normal end diastolic length and operate on the lower part of the ascending limb of the Frank Starling curve The high EDP is a consequence of extrinsic compression and the fibers are underloaded despite the high filling pressure Theoretically the fibers need to generate less tension and perform less work but the constricting shell which infiltrates the epicardium also

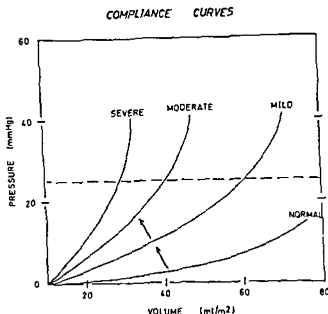


Fig 17 Diastolic pressure volume curves for normal subjects and for patients with mild moderate and severe restriction of the ventriculo-pericardial system At a critical venous filling pressure (*dashed line*) important clinical symptoms occur and the patients seek medical care regardless of their end-diastolic volume and compliance

in the LV but this is not related to the EDV Every diastolic pressure volume curve is exponential and the rate of pressure rise during ventricular filling depends on four factors the slope of the curve the level of the diastolic pressure the end diastolic volume and the absolute volume change At high diastolic pressures the curves have a steep slope so that changes in pressure and stroke volume overshadow the effect of changes in compliance or end diastolic volume

There may also be time dependent changes due to viscous inertial or plastic properties of the pericardium we have not measured these changes in the present study Similarly we have no information on the influence of the high end-diastolic pressure on coronary blood flow but we presume it to be normal in the absence of coronary artery disease

Summary

Left ventricular function was studied in systole and diastole in 30 patients with constrictive pericarditis Left ventricular end-diastolic volume was used to divide the patients into three arbitrary groups severe constriction (EDV < 25 ml /M²) moderate constriction (EDV 25 to 50 ml /M²) and mild constriction (EDV > 50 ml /M²)

The patients had high ventricular diastolic and venous filling pressures (mean LVEDP = 23 ± 7 mm Hg mean RVEDP = 20 ± 7 mm Hg) Measurements related to *absolute* fiber shortening (stroke index stroke work index and left ventricular ejection rate) were reduced and linearly related to the degree of constriction as assessed by the end-diastolic volume

Measurements of *relative* fiber shortening or lengthening (ejection and filling fraction and circumferential fiber shortening) were normal despite great reduction in ventricular volumes

Velocity measurements peak LV dp/dt and mean velocity of circumferential fiber shortening were normal or slightly reduced

These changes were reflected in the systolic time interval measurements pre ejection phase left ventricular ejection time and the ratio PEP/LVET

Diastolic function of the ventricle was abnormal the distensibility index of the ventriculo pericardial system (ΔV/ΔP) was low and the passive elastic modulus in increased The change in compliance corre

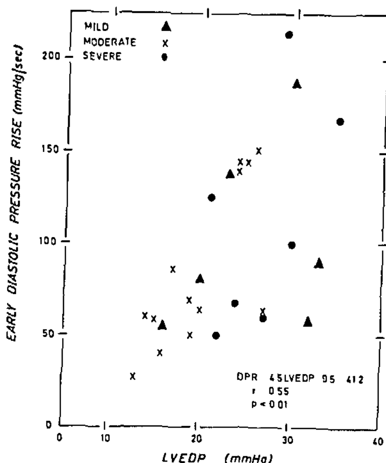


Fig 16 Relationship between the rate of pressure rise in early diastole (*DPR*) and LV end diastolic pressure (*EDP*) DPR was related to the LVEDP regardless of the severity of constriction assessed by angiography

$$\Delta P/\Delta V = a\bar{P} + b$$

The measurement does not need measured angiographic volumes and expresses compliance in terms of changes in intraventricular diastolic pressure (ΔP) and stroke volume (ΔV) The passive elastic modulus was abnormal in constrictive pericarditis and increased with the severity of constriction It is noteworthy that in severe constriction $\Delta P/\Delta V$ and the passive elastic modulus of the pericardium were lower than corresponding measurements of diastolic function of the myocardium in a group of patients with acute myocardial infarction [21]

Our concept of the diastolic function of the ventricle in health and disease is shown schematically in Fig 17 There appears to be a family of diastolic pressure volume curves for normal subjects and for patients with cardiac disease Every patient is in a condition of circulatory equilibrium which is determined at any instant by the degree of constriction, the ventriculo pericardial compliance the stroke output and the venous filling pressure As the disease progresses and compliance falls the patient moves from curve to curve Important signs and symptoms of systemic venous hypertension become clinically apparent at a critical venous pressure and the patient seeks medical care regardless of the severity of constriction, the abnormality of compliance and the reduction in ventricular volume This accounts for the similarity in the ventricular diastolic pressures in this group of patients We did not investigate patients with mild constrictive pericarditis and it is possible that in the early phase of the disease the diastolic filling pressures which are much lower may be related to the severity of constriction In established disease the diastolic pressures are similar they do not correlate with the degree of constriction assessed by angiocardiography and cannot be used to differentiate the severity of the constricting process

Patients with a high EDP also have a rapid rate of pressure rise in earl astole

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lated with the degree of constriction and there was a linear relationship between compliance and EDV

The ventricle was underloaded despite the high filling pressure and stroke work index was reduced extrinsic compression raised the diastolic pressure and reduced left ventricular volumes

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used in this investigation are presented elsewhere [18])

Methods

The corrected orthogonal leads of 120 normal subjects were recorded on magnetic tape using the axial lead system of McFee and Parungao In order to determine if these subjects were free of heart disease each was given a clinical examination (Table I) including measurement of his blood pressure cardiac auscultation and evaluation by palpation and percussion Histories of these subjects were also studied in an effort to detect any previous cardiovascular problems

The details of procedures utilized in recording and signal processing were reported in an earlier paper [18] A total of 63 measurements were made from the digitized wave forms The results of the analysis of these measurements are reported in Tables II through V

Thirty six of the 63 distributions of the measurements differed significantly ($p < 0.01$) from normality some because of skewness alone and others because of skewness and kurtosis Logarithmic and linear transformations were performed on those measurements whose distributions were skewed * The means and confidence limits of the transformed data were then computed These estimates were then retransformed to the linear scale and the results were reported Twenty five of the 36 nonnormal distributions thus transformed were not significantly different ($p < 0.01$) from the Gaussian curve

Two of the remaining 11 non Gaussian distributions were significantly different ($p < 0.01$) from normality because of kurtosis The direction of *terminal deflection* of the QRS loop in the frontal plane was platykurtic i e widely scattered and somewhat flat the *mean is reported in* Table III The distribution of the direction of the 40 msec vector of the QRS loop in

Table I *Distribution of subjects by age and sex*

Age (yrs)	*Male*	*Female*	*Total*
15 to 24	22	25	47
25 to 34	34	18	52
35 to 44	3	9	12
45 to 54	2	6	8
55 to 64	0	1	1
Total	61	59	120

the left sagittal plane was found to be leptokurtic (highly peaked) The mean and 95 per cent confidence limits of this distribution are reported however since it was felt that this information was still valuable and consistent with the data

Transformation of the 9 remaining non Gaussian distributions (the direction of the maximum P vector in all three planes the direction of terminal deflection of the QRS loop in the horizontal plane the magnitude of the 60 msec vector in the QRS loop QRS duration *the magnitude of* the S T vector in the left sagittal plane and the direction of the maximum T_P vector in *both the frontal and left sagittal planes)* did not eliminate the problems of non normality therefore the medians and *ranges of these data are reported in Table* II

The recommendations for reference axes *of the Committee on Electrocardiography* of the American Heart Association were followed with one exception The zero position on the left sagittal reference frame was transposed to the patient s anterior The numerical data thus obtained are the same as if the right sagittal reference frame had been used and can be compared readily to the normal values reported by Chou and Helm[19] and Macfarlane and associates [7]

Results

The statistics which summarize the data are shown in Tables II through V An inspection of these tables will reveal that some of the distributions were Gaussian in form and required no transformation however a majority of the measurements were non Gaussian The logarithmic transformation procedure made most of these non

* If th d t were k wed t th right ... b t ry ... t t ... dd d t ... sure that ll ... be g ... t than ze o d the log ri hm were then t ken. If th dat were k wed t th left th d ta were fi t m lt pli d by −1 and the tra sf m d i th same m ne Retra sf rma tio of the p ramete stim te would then i cl d taki g the t log f th m ... nd limits, bt cti g ny t t th t h d bee dded d m ltiply g by −1 if the d ta were kewed to the left

The McFee-Parungao (axial) vectorcardiogram in normal subjects

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The McFee Parungao (axial) vector cardiographic lead system[1] has been shown to have theoretical advantages over other vectorcardiographic lead systems now in use [2-4] Recently, Lawrie and Macfarlane[5] reported that in clinical application, the axial lead system correlated more favorably with an ideal orthogonal lead system than did the widely used Frank system Macfarlane[6] modified the axial lead system by means of the Brody Arzbaecher lead strength equalization and published the results of extensive clinical trials using this modification [7,8] Gamboa and White[9,10] and Ainger[11,12] studied several lead systems in infants including the axial, and the results of these investigations continue to appear in the literature The purpose of this paper is to present estimates of the parameters of the unmodified axial vector cardiograms in normal adults

Comparisons among lead systems are difficult for two reasons First because many electrocardiographic measurements are non Gaussian in distribution, the determination of means and 95 per cent confidence limits for given measurements in electrocardiography and vectorcardiography has been difficult To avoid this problem some authors present ranges while others disregard the distributions of the data and calculate 95 per cent confidence limits Second, comparison of parameter estimates is sometimes difficult because data are measured in different ways For example some workers[13-16] report values measured at the change of direction of the vector loop while most workers in this country and Europe report values obtained at various timed intervals after the onset of the loop Downs and Liebman,[17] and Ainger[11,12] indicate that linear methods of reporting and analyzing angular data are incorrect and treat vector quantities as points on a circle or a sphere

In this study, yet another method for presentation of the vectorcardiographic data is used logarithmic transformations have been applied to those planar vector cardiographic values whose distributions are not Gaussian (Descriptive statistics for some of the untransformed data

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Table IV The direction and magnitude of the junctional (S T) vector in normal subjects

S T vector	Hori ontal plane		Frontal plane		Left sagittal plane	
	Mean	95% Conf lmts	Mean	95% Conf lmts	Mean	95% Conf lmts
Magnitude (mv)	0 50	0 24 to 1 01	0 50	0 27 to 0 93†	0 38	0 07 to 0 91†
Direction (degrees)	+29	−4 to +61	+31	+10 to 52	+49	+5 to +93

Me and 95 pe ce t confid ce limit comp ted usi g logarithmic transformati n
†Median a d r ge report d

Table V The direction and magnitude of the maximum T vector in normal subjects

T vector	Hori ontal plane		Frontal plane		Left sagittal plane	
	Mean	95% Conf lmts	Mean	95% Conf lmts	Mean	95% Conf lmts
Maximum T vector						
Magnitude (mv)	0 53	0 25 to 1 15	0 51	0 25 to 1 02	0 39	0 14 to 1 10
Direction (degrees)	+33	0 to +66	+31	+9 to +53	+42	+2 to +83
T duration (msec)	284	232 to 336				
Maximum T_P vector						
Magnitude (mv)	0 03	0 01 to 0 07	0 04	0 02 to 0 09	0 04	0 02 to 0 09
Direction (degrees)	−119	+133 to −11	−110†	+47 to 0†	−118†	−177 to +62†

M and 95 pe cent confidence limits computed by us g th logarithmi tra sform tio
†Med a d ra ge reported

Table VI Lead strengths of the modified and original axial lead systems also the Frank lead system

System	X	Y	Z
Axial	1 61	1 48	2 24 mv /cm
Modified axial	1 48	1 48	1 48
Frank	1 45	1 40	1 37

in comparison with the QRS and T loops Generally the P loop tends to be inscribed counterclockwise in the horizontal and left sagittal planes In the frontal plane the loop is even more variable and a figure of eight configuration is frequently seen

The QRS loop Nearly all the QRS loops were inscribed counterclockwise in the horizontal and left agittal planes (95 per cent in each plane) In these two planes those loops (7 per cent in each plane) which present a figure-of eight morphology were predominantly counterclockwise the initial portion of those loops was always counterclockwise in this series and the change of direction which produced the figure-of eight occurred distal from the ori gin of the loop and near the site of the maximum instantaneous vector Details of these loops are presented in Table III Generally the values are larger than similar values reported with the Frank system or with the modified axial lead system this is especially true of the 40 millisecond 60 millisecond and maximum instantaneous vectors

The direction of the initial deflection is of interest in the three planes In the hori zontal plane the mean direction was 106 degrees (anterior and slightly to the right) with limits from 41 to 158 degrees It can thus be said that the initial vector in the horizontal plane always moves in an an

Table II *The direction and magnitude of the maximum P vector in normal subjects*

Parameter	*Hori ontal plane*		*Frontal plane*		*Left sagittal plane*	
	Mean	*95% Conf lmts*	*Mean*	*95% Conf lmts*	*Mean*	*95% Conf lmts*
Maximum P vector						
Magnitude (mv)	0 08	0 05 to 0 14	0 13	0 06 to 0 2	0 12	0 04 to 0 21
Time of occurrence (msec)	64	35 to 94	55	32 to 78	50	23 to 78
Direction (degrees)	−5†	−100 to +161†	+66†	−46 to +107†	+82†	−165 to +119†
P duration (msec)	94 0*	75 to 118*				

*Mean and 95 per cent confidence limits computed using logarithmic transformation
†Median and range reported

Table III *Characteristics of the normal QRS loop*

Characteristic	*Hori ontal plane*		*Frontal plane*		*Left sagittal plane*	
	Mean	*95% Conf lmts*	*Mean*	*95% Conf lmts*	*Mean*	*95% Conf lmts*
Maximum QRS vector						
Magnitude (mv)	1 61*	0 94 to 2 78*	1 97	1 01 to 2 92	1 48	0 62 to 2 34
Direction (degrees)	−17*	−120 to +38*	+39	+10 to +69	+119	+40 to −161
Time of occurrence of max QRS vector (msec)	46*	34 to 63*	43*	35 to 54*	47*	34 to 64*
20 msec vector						
Magnitude (mv)	0 43*	0 16 to 1 13*	0 16*	0 03 to 0 76*	0 40*	0 15 to 1 08*
Direction (degrees)	+78	+30 to +126	0	−163 to +163	+4	−37 to +45
40 msec vector						
Magnitude (mv)	1 42	0 52 to 2 32	1 68	0 64 to 2 73	1 16	0 33 to 1 98
Direction (degrees)	−5*	−73 to +38	+38	+5 to +71	+98*	+23 to +156*
60 msec vector						
Magnitude (mv)	0 79†	0 13 to 2 14†	0 31*	0 06 to 1 61*	0 72*	0 23 to 2 28*
Direction (degrees)	−89	−137 to −26*	−7	All quadrants	+178*	+114 to −129
Direction of initial deflection (degrees)	+106*	+41 to +158	−138*	+81 to −31	+20*	−69 to +56*
Direction of terminal deflection (degrees)	−95†	All quadrants	−43*	All quadrants	−169	+107 to −85
Direction of inscription	93% Counterclockwise 7% Figure of eight		36% Clockwise 43% Figure of eight 21% Counterclockwise		7% Figure of eight 93% Counterclockwise	
QRS duration (msec)	94†	70 to 142†				

*Mean and 95 per cent confidence limits computed using logarithmic transformation
†Median and range reported

normal distributions Gaussian (these are indicated by one asterisk in the tables) and permitted the computation of valid 95 per cent confidence limits A third group of data could not be transformed to a normal distribution (indicated by a dagger) For this group only ranges and medians are reported

The P loop The atrial loop does not close because the atrial T deflection, which is normally opposite in sign from the P wave in orthogonal and scalar leads begins be fore the end of the atrial depolarization process The P loop is very irregular in contour and is so small that considerable amplification is required to visualize it well

Table IV The direction and magnitude of the junctional (S T) vector in normal subjects

S-T vector	Horizontal plane		Frontal plane		Left sagittal plane	
	Mean	95% Conf lmts	Mean	95% Conf lmts	Mean	95% Conf lmts
Magnitude (mv)	0 50	0 24 to 1 01	0 50	0 27 to 0 93†	0 38	0 07 to 0 91†
Direction (degrees)	+29	−4 to +61	+31	+10 to 52	+49	+5 to +93

Mean nd 95 per ce t confide ce l m ts comp ted usi g logarithmic tra sformation.
†Median and rang reported

Table V The direction and magnitude of the maximum T vector in normal subjects

T vector	Horizontal plane		Frontal plane		Left sagittal plane	
	Mean	95% Conf lmts	Mean	95% Conf lmts	Mean	95% Conf lmts
Maximum T vector						
Magnitude (mv)	0 53	0 25 to 1 15	0 51	0 25 to 1 02	0 39	0 14 to 1 10
Direction (degrees)	+33	0 to +66	+31	+9 to +53	+42	+2 to +83
T duration (msec)	284	232 to 336				
Maximum T_P vector						
Magnitude (mv)	0 03	0 01 to 0 07	0 04	0 0? to 0 09	0 04	0 02 to 0 09
Direction (degrees)	−119	+133 to −11	−110†	+47 to 0†	−118†	−177 to +62†

Mea nd 95 pe cent co fidence limits comp t d by u ing the logarithmi t sfo mat on
†Media and rang reported

Table VI Lead strengths of the modified and original axial lead systems also the Frank lead system

System	X	Y	Z
Axial	1 61	1 48	2 24 mv /cm
Modified axial	1 48	1 48	1 48
Frank	1 45	1 40	1 37

in comparison with the QRS and T loops Generally the P loop tends to be inscribed counterclockwise in the horizontal and left sagittal planes In the frontal plane the loop is even more variable and a figure of eight configuration is frequently seen

The QRS loop Nearly all the QRS loops were inscribed counterclockwise in the horizontal and left agittal planes (95 per cent in each lane) In these two planes those loops (7 per cent in each plane) which present a figure-of eight morphology were predominantly counterclockwise the initial portion of those loops was always counterclockwise in this series and the change of direction which produced the figure of-eight occurred distal from the ori gin of the loop and near the site of the maximum instantaneous vector Details of these loops are presented in Table III Generally the values are larger than similar values reported with the Frank system or with the modified axial lead system this is especially true of the 40 millisecond 60 millisecond and maximum instantaneous vectors

The direction of the initial deflection is of interest in the three planes In the hori zontal plane the mean direction was 106 degrees (anterior and slightly to the right) with limits from 41 to 158 degrees It can thus be said that the initial vector in the horizontal plane always moves in an an

Table VII *P loop, maximum P vector*

Source	Transverse plane		
	Direction (degrees)	Magnitude (mv)	Time (msec)
Chou and Helm (Frank)			
Mean	−5	0 07	
95% Ranges	−50 to 60	0 04 to 0 10	
Macfarlane et al (Modified axial)			
(a) Up through 14 yrs			
Mean and S D	21 ± 50	0 09 ± 0 03	
96% Ranges	−46 to 101	0 06 to 0 14	
(b) 15 to 29 yrs			
Mean and S D	25 ± 53	0 08 ± 0 03	
96% Ranges	2 to 165	0 03 to 0 16	
(c) > 29 yrs of age			
Mean and S D	3 ± 54	0 08 ± 0 03	
96% Ranges	2 to 103	0 04 to 0 14	
Present study (Axial)			
Mean	−5†	0 08	64
95% Conf lmts	−100 to 161†	0 05 to 0 14	35 to 94
P duration (msec)	94 0*	75 to 118*	

*Mean and 95 per cent confidence limits were computed using logarithmic transformation

†Median and range reported

Table VIII *QRS loop, maximum QRS vector*

Source	Transverse plane		
	Direction (degrees)	Magnitude (mv)	Time (msec)
Chou and Helm (Frank)			
Mean	−10	1 3	38
96% Ranges	−80 to 20	0 85 to 1 95	30 to 48
Macfarlane et al (Corrected axial)			
(a) Up through 14 yrs			
Mean and S D	−25 ± 56	1 34 ± 0 45	
95% Ranges	−125 to 40	0 81 to 2 07	
(b) 15 to 29 yrs			
Mean and S D	−11 ± 26	1 15 ± 0 34	
96% Ranges	−88 to 30	0 52 to 1 98	
(c) 30 yrs and older			
Mean and S D	−5 ± 24	1 12 ± 0 33	
96% Ranges	−82 to 23	0 59 to 1 89	
Present study (Axial)			
Mean	−17*	1 61*	46*
95% Conf lmts	−120 to 38*	0 94 to 2 78*	34 to 63*

*Mean and 95 per cent confidence limits computed by use of logarithmic transformation

terior direction but may be either to the left or right In the frontal plane the mean direction of the initial deflection was −138 degrees, with limits of −31 to 81 degrees confirming the left to right direction tend ency and the greater variability of measurements in the frontal plane In the left sagittal plane the mean direction of the initial vector was 20 degrees with limits from −69 to 56 degrees tha h initial

Sagittal plane			*Frontal plane*		
Direction (degrees)	*Magnitude (mv)*	*Time (msec)*	*Direction (degrees)*	*Magnitude (mv)*	*Time (msec)*
85 50 to 110	0 12 0 04 to 0 18		65 15 to 90	0 12 0 06 to 0 20	
47 ± 64 −60 to 108	0 12 ± 0 04 0 04 to 0 19		40 ± 45 −20 to 70	0 13 ± 0 04 0 09 to 0 17	
64 ± 45 41 to 108	0 13 ± 0 06 0 04 to 0 25		49 ± 42 27 to 99	0 13 ± 0 06 0 05 to 0 25	
86 ± 41 −129 to 1	0 14 ± 0 06 0 06 to 0 27		62 ± 36 −8 to 99	0 15 ± 0 05 0 06 to 0 28	
82† −165 to 119†	0 12 0 04 to 0 21	50 23 to 78	66† −46 to 107†	0 13 0 06 to 0 2	55 32 to 78

Sagittal plane			*Frontal plane*		
Direction (degrees)	*Magnitude (mv)*	*Time (msec)*	*Direction (degrees)*	*Magnitude (mv)*	*Time (msec)*
100 50 to 165	1 0 0 3 to 1 9	Same Same	35 10 to 65	1 5 0 9 to 2 2	Same Same
102 ± 30 52 to 155	1 33 ± 0 40 0 70 to 1 93		45 ± 14 27 to 62	1 74 ± 0 54 0 99 to 2 41	
110 ± 33 64 to −151	1 24 ± 0 45 0 59 to 2 16		45 ± 14 17 to 74	1 61 ± 0 44 1 00 to 2 64	
109 ± 42 49 to −50	0 91 ± 0 32 0 47 to 1 63		35 ± 19 0 to 63	1 37 ± 0 38 0 79 to 2 29	
119 −161 to 40	1 48 0 62 to 2 34	47 34 to 64	39 10 to 69	1 97 1 01 to 2 92	43* 35 to 54

deflection should be anterior and may be directed either up or down

The S T (junctional) vector and the T vector The statistics for these two vectors are included in Tables IV and V to show their relationship to the vectorcardio graphic loop as well as to the scalar electro cardiogram The T loop is slowly inscribed It is generally smooth in contour as is the QRS loop The T loop is nearly always in

Table IX Normal QRS loop

Source	Transverse plane		Sagittal plane		Frontal plane	
	Direction (degrees)	Magnitude (mv)	Direction (degrees)	Magnitude (mv)	Direction (degrees)	Magnitude (mv)
			20 msec Vector			
Chou and Helm (Frank)						
Mean	55	0 40	15	0 30	20	0 30
95% Ranges	0 to 120	0 15 to 0 75	−30 to 75	0 1 to 0 55	All quadrants	0 05 to 0 7
Present study (Axial)						
Mean	78	0 43*	4	0 40*	0	0 16*
95% Conf lmts	30 to 126	0 16 to 1 13*	−37 to 45	0 15 to 1 08*	−163 to 163	0 03 to 0 76*
			40 msec Vector			
Chou and Helm (Frank)						
Mean	−20	1 15	110	0 9	35	1 25
95% Ranges	−90 to 25	0 55 to 1 9	60 to 170	0 25 to 1 8	−10 to 70	0 4 to 2 2
Present study (Axial)						
Mean	−5*	1 42	98*	1 16	38	1 68
95% Conf lmts	−73 to 38*	0 52 to 2 32	23 to 156*	0 33 to 1 98	5 to 71	0 64 to 2 73
			60 msec Vector			
Chou and Helm (Frank)						
Mean	−90	0 45	160	0 55	85	0 25
95% Ranges	−125 to −35	0 0 to 0 9	115 to −40	0 1 to 1 0	All quadrants	0 0 to 0 6
Present study (Axial)						
Mean	−89*	0 79†	178*	0 72*	−7	0 31*
95% Conf lmts	−137 to −26*	0 13 to 2 14†	114 to −129*	0 23 to 2 28*	All quadrants	0 06 to 1 61*

*Mean and 95 per cent confidence limits computed using logarithmic transformation
†Median and range reported

scribed in the same direction as the QRS loop in the normal individual however there was an occasional subject in the sample for whom this was not the case

Discussion

Presented in Table VI are the lead strengths in millivolts per centimeter for the axial modified axial and Frank lead systems In Tables VII through X the data obtained in the present study are compared with the data reported by Chou and Helm[19] (Frank lead system) and by Macfarlane and co workers[7] (modified axial lead system) Although the present study uses the left sagittal reference frame while the other two studies use the right sagittal the numerical data should be comparable since the polarity of the abscissa is reversed The data in this report and in Macfarlane s were translated to allow degrees to be reported to plus 180 degrees and minus 180 degrees

The data in Tables VII VIII, and X reflect Macfarlane s three groups of data (a) up through 14 years (b) 15 through 29 years and (c) 30 years and over

Chou and Helm reported their data with means and 95 per cent ranges while Macfarlane and colleagues reported means standard deviations and 96 per cent ranges

It is apparent that the greater lead strengths of the axial (McFee Parungao) lead system are more manifest in the QRS loop than in either the P or T loop This is in accordance with the observed greater size or more rotund appearance of the axial QRS loops The observation that the 40 millisecond 60 millisecond and maximum instantaneous vectors are all substantially greater in the axial system is

Table X T loop maximum T vector

Source	Transverse plane		Sagittal plane		Frontal plane	
	Direction (degrees)	Magnitude (mv)	Direction (degrees)	Magnitude (mv)	Direction (degrees)	Magnitude (mv)
Chou and Helm (Frank)						
Mean	35	0 5	45	0 4	35	0 5
95% Ranges	0 to 65	0 25 to 0 75	20 to 90	0 2 to 0 7	20 to 55	0 25 to 0 75
Macfarlane et al (Corrected axial)						
(a) Up through 14 yrs						
Mean and S D	12 5 ± 17	0 44 ± 0 21	76 ± 21	0 29 ± 0 17	32 ± 13	0 50 ± 0 23
96% Ranges	−5 to 36	0 24 to 0 83	46 to 106	0 14 to 0 59	15 to 54	0 26 to 0 94
(b) 15 to 29 yrs						
Mean and S D	30 ± 21	0 35 ± 0 13	58 ± 23	0 32 ± 0 13	41 ± 20	0 41 ± 0 14
96% Ranges	−8 to 78	0 15 to 0 64	27 to 102	0 14 to 0 62	17 to 70	0 18 to 0 78
(c) 30 yrs and older						
Mean and S D	29 ± 23	0 31 ± 0 11	59 ± 22	0 30 ± 0 11	42 ± 18	0 36 ± 0 12
96% Ranges	−3 to 71	0 13 to 0 56	25 to 92	0 14 to 0 54	15 to 68	0 16 to 0 59
Present study (Axial)						
Mean	33	0 53	42	0 39	31	0 51
95% Conf lmts	0 to 66	0 25 to 1 15	2 to 83	0 14 to 1 10	9 to 53	0 25 to 1 02*
T duration (msec)	284					
	232 to 336					

*Th 95 pe ce t confid ce limits were computed by using th l garithmic transformation.

of obvious importance in deriving any voltage criteria for ventricular hyper trophy The modified axial values fall gen erally between the axial and the Frank values and indeed the published modified axial loops closely resemble Frank loops rather than unmodified axial loops As far as the planar projections of the maximum instantaneous P vector are concerned the mean magnitudes in all the reports are in close agreement (Table VII)

The 20 40 and 60 millisecond vectors of the QRS in this study are compared in Table IX with those reported by Chou and Helm for the Frank system With one exception the mean magnitude of the 20 millisecond vector in the frontal plane the mean values of the unmodified axial lead system were again larger than those of the Frank lead system

Although transformation of nonnormal data is a fairly common statistical pro cedure[20] vectorcardiographers appear not to have used this method of obtaining means and 95 per cent confidence limits for skewed electrocardiographic distributions Failure to transform data whose distribu tions are skewed leads to incorrect confi dence limits and the clinician could con clude from using these incorrect limits that a subject was outside normal limits when he was not

Summary

Sixty three parameter estimates from the McFee Parungao (axial) vectorcardio grams of 120 normal subjects were com puted and tested for normality Thirty six of these distributions were found to differ significantly ($p < 0.01$) from Gaussian distribution Logarithmic transformations were performed on those measurements whose distributions were nonnormal and it was found that all but nine distributions so treated did not differ significantly from the Gaussian distribution

Thirty nine of the 63 measurements were compared with electrocardiographic data from the modified axial and Frank lead systems Lead strengths for the QRS vector in the axial system were larger than those for the other two systems This difference

Table IX Normal QRS loop

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Chou and Helm (Frank)						
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95% Ranges	−125 to −35	0 0 to 0 9	115 to −40	0 1 to 1 0	All quadrants	0 0 to 0 6
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Mean	−89*	0 79†	178*	0 72*	−7	0 31*
95% Conf lmts	−137 to −26*	0 13 to 2 14†	114 to −129*	0 23 to 2 28*	All quadrants	0 06 to 1 61*

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Experience with the coronary artery bypass graft in a community hospital

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Although the coronary artery bypass graft (CABG) now accounts for about one half of all open heart operations [1] it remains an experimental procedure [2] Many of the reports which are available have come from a relatively limited number of large institutions where the technique has been developed and a large volume of work done The future role of the operation will become better defined as a broader experience from more and different types of institutions is obtained The purpose of this paper is to review the hospital course of patients undergoing CABG in a large private hospital

Case material and results

Fifty five patients were submitted to the CABG procedure Eleven died and 44 were discharged from the hospital giving an early mortality rate of 20 per cent Table I compares some clinical features of the two groups The average age of the survivors was 53 and of the nonsurvivors 63 years Forty two of the 55 patients were men The average clinical class using the New York Heart Association classification was 3 0 for those who lived and 3 5 for those who did not Statistical analysis by the t test showed that there was no difference in clinical class between the two groups at the 0 10 level of significance

A history of congestive heart failure and probably also systemic hypertension occurred more frequently in the nonsurvivors However the incidence of a history of diabetes mellitus hyperlipidemia or a previous myocardial infarction was about the same in both groups

Table II compares some angiographic features of the surviving and nonsurviving patients All patients had at least one major coronary artery with a luminal narrowing of 50 per cent or more The survivors had an average of 2 1 coronary arteries per patient demonstrating a luminal narrowing of at least 50 per cent compared with 2 4 for the nonsurvivors The presence of mitral insufficiency and abnormalities of the wall of the left ventricle and of its contraction were frequent in both groups

Table III shows that 77 grafts were done in the 44 survivors and 20 in the 11 nonsurvivors giving an average number of grafts per patient of 1 75 and 1 82 respectively Statistical analysis by the t test showed that there was no difference in the average number of grafts per patient between the two groups at the 0 20 level of

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resulted in the axial system s having greater mean planar projections for the 40 milli second 60 millisecond, and maximum in stantaneous QRS vectors than either of the other two systems There are few differ ences in P and T loops among the three, and the directions of inscription are similar for the three systems As far as magnitude is concerned, the QRS values for the modi fied axial lead system fall between the values for axial and Frank lead systems

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Table III Comparison of surgical aspects of surviving and nonsurviving patients with coronary artery bypass grafts (55 patients)

	Total no of grafts		Av no grafts per pt	Removal of LV wall		Vineberg procedure	Valvular surgery	
Survivors (44)	Saphenous vein	68	1 5	Resection of wall	7	1	Plicate mitral valve	1
	Internal mammary	9		Plication of aneurysm	1		Replace mitral and aortic valves	1
	Total	77		Total	8		Total	2
Nonsurvivors (11)	Saphenous vein	19	1 8			0	Replace mitral valve	2
	Internal mammary	1					Mitral commissurotomy	1
							Replace aortic valve	1
	Total	20					Total	4

Table IV Major complications associated with coronary artery bypass grafts (49 patients)

Complication	Complication rate (no of patients)	% [No of pts with complications ÷ total (49 patients)]
Complications		
Pulmonary emboli	10	20
Myocardial infarction	9	18
Brain damage	9	18
Postoperative hemorrhage	7	14
Cardiac arrest	5	10
Serum hepatitis	3	6
Renal failure	2	4
Subtotal	45	
Miscellaneous major complications		
Chronic heart failure	2	
Tracheostomy	2	
Permanent pacemaker	1	
Postperfusion syndrome	1	
Gastrostomy	1	
Wound infection (death)	1	
Pneumonia	1	
Ulnar neuropathy (requiring surgery)	1	
Subtotal	10	
Total number of major complications	55	

there were 35 major complications and six deaths Over the last 15 month period 21 patients had CABG surgery and there were 20 major complications and five deaths

Angiograms were done two to three weeks postoperatively on 27 of the 44 patients who survived the operations Table VI shows that 71 per cent of the saphenous vein and 78 per cent of the internal mammary grafts were patent The over all patency rate was 44 out of 61 or 72 per cent

The data suggest that a myocardial infarction may be associated with the CABG procedure even though one or more grafts remain patent Five patients who had sustained an operative myocardial infarction were studied by angiography Three of these patients each had received a single graft and in two the graft was patent

Table I Comparison of clinical characteristics of surviving and nonsurviving patients with coronary artery bypass grafts (55 patients)

	No of patients	Sex M/F	Av age (yr)	Clinical class						History of*				
				1	2	3	4	?	Av	Heart failure	Hyper tension	Hyper lipidemia	Diabetes mellitus	Previous MI
Survivors	44	35/9	53	5	6	12	19	2	3 0	6/41	11/42	19/42	5/42	22/43
Nonsurvivors	11	7/4	63	1	0	2	7	1	3 5	5/10	4/10	2/10	2/10	5/9

*Ratio of patients with positive history to total number of patients with known history

Table II Comparison of angiographic features of surviving and nonsurviving patients with coronary artery bypass grafts (55 patients)

	Greater than 50% narrowing of major coronary artery*		Abnormal LV contraction	Discrete LV aneurysm	Mitral insufficiency
	No of involved arteries	No of patients			
Survivors (44)	1	7	29	6	14
	2	24			
	3	13			
Nonsurvivors (11)	1	2	6	3	5
	2	2			
	3	7			

*Right coronary artery left circumflex coronary artery left anterior descending coronary artery

significance One of the survivors had an internal mammary artery implanted (Vineberg operation) as an additional procedure Noncontracting areas of the left ventricular wall were removed in eight of the survivors but *in none* of the nonsurvivors Valvular surgery was also done in two of the survivors and in four of the nonsurvivors

Table IV summarizes what were considered to be the major postoperative complications excluding death Six patients died on the operating table Fifty five major complications were found in the remaining 49 patients In this group 15 patients had one major complication six had two five had three two had four and one patient had five complications There were five postoperative deaths Of the 44 patients who survived 20 had no major complication

The major complications most frequently recognized were pulmonary emboli (ten patients) myocardial infarction (nine patients) severe brain damage (nine patients) severe postoperative hemorrhage (five of the seven patients required reoperation) and cardiac arrest (five patients) As classified in Table IV there were 10 miscellaneous major complications It was of interest that two patients had no cardiac failure before operation but suffered from chronic congestive failure postoperatively

Complications considered as minor are summarized in Table V There was a total of 28 patients who had 17 different minor complications Nine of the 44 patients who survived had neither a major nor minor complication

The 55 patients were operated upon over a 30 month interval In the first half of this period 34 patients had operations and

urgery and to a lesser degree a history of systemic hypertension However a history of hyperlipidemia diabetes mellitus or previous myocardial infarction was not more frequent in the nonsurvivors than the survivors

Table III shows that details of the operation did not appear to distinguish the CABG survivors from the nonsurvivors The average number of grafts done per patient was not statistically different in the two groups

Major postoperative complications were frequent as summarized in Table IV The most frequently recognized major complications included pulmonary emboli myocardial infarction severe brain damage major postoperative hemorrhage and cardiac arrest Table V shows that a wide variety of what were classified as minor complications also occurred Nine of the 44 patients who survived had neither a major nor a minor complication

The complications which are tabulated were those observed during regular clinical care It is probable that a comprehensive search in the patients would have revealed other complications For example although pulmonary emboli were frequently diagnosed the incidence might have been greater had each patient been specifically studied

Both the mortality rate and the frequency of major complications were essentially unchanged for the first and last 15 months of the study In this series increasing surgical experience did not appear up to this time to reduce the immediate risks However it is possible that continued experience might produce improved results

Table VI shows that the average early graft patency rate was 72 per cent There appeared to be no particular difference for patency rate between the saphenous vein and the internal mammary grafts although this is not certain because the latter group was small in number It appeared possible that the placement of a CABG might be associated with accelerated closure of a stenotic coronary artery Others have also reported this finding[3] The patency of the graft apparently did not provide protection against a myocardial infarction complicating the operation

Table VI Results of early postoperative angiograms of patients with coronary artery bypass grafts (27 patients)

Type of graft	No of grafts done	No of grafts patent	Per cent of grafts patent
Saphenous vein	52	37	71
Internal mammary	9	7	78
Total	61	44	72

Although the tables statistically summarize the results observed in the patients undergoing CABG they do not adequately solve the physician s problem when he is faced with the decision of medical vs surgical treatment As far as the immediate surgical procedure is concerned the practicing physician wishes to know not only his patient s chances of survival but also the postoperative hazards The following analysis illustrates one approach to arriving at a clinician s overview of the operation for this series of patients

If we assume that the value of the CABG is to supply otherwise unavailable blood to the myocardium in this series the operation was an immediate failure for those patients who died (11 patients) plus those known to have no patent graft (five patients) Adding from the remaining 39 patients the seven who had a myocardial infarction associated with the operation gives a cumulative failure rate of 23/55 or 42 per cent Assuming that all the remaining 32 patients will have patent grafts and that all will achieve the full theoretical value of the operation they must still run the gauntlet of major complications Three patients had severe brain damage and of the remaining 29 two had cardiac arrest Of the remaining 27 two had severe postoperative hemorrhage of the 25 four had pulmonary emboli of the 21 one had serum hepatitis Thus the patient submitted for CABG had about two chances out of three of either dying having no patent graft or having a life threatening postoperative complication

Although the experience with the CABG in this series seems relatively clear there

Table V Minor complications associated with coronary artery bypass grafts (49 patients)

Complication	Complication rate (no of patients)
Femoral vein or artery thrombosis (requiring surgery)	2
Heart failure	2
Wound infection	2
Wound dehiscence	2
Phlebothrombosis	2
Hematoma of groin (requiring surgical drainage)	2
Respiratory insufficiency (requiring reintubation)	2
Urinary tract infection	1
Pericarditis	1
Postpericardiotomy syndrome	1
Ileus	1
Nonunion of sternum (requiring surgery)	1
Acute depression	1
Fever of unknown origin	1
Atelectasis and pleural effusion	1
Arrhythmias (requiring treatment)	
Sinus arrest with syncope	1
Atrial fibrillation and flutter (producing hypotension)	2
Premature ventricular contractions (frequent runs)	1
Supraventricular tachycardia and arrhythmias	1
Ulnar neuropathy	1
Total	28

Three grafts had been placed in the fourth patient and two were open In the remaining case three of four grafts were patent yet the patient had had a large inferior and anteroseptal myocardial infarction followed by chronic severe cardiac failure

Postoperative angiograms provided some evidence to suggest that progressive narrowing might occur in a stenotic coronary artery which was grafted This was noted in two patients mentioned above who had had a myocardial infarction associated with a single graft the graft later being shown to be patent Preoperatively the degree of narrowing of the right coronary artery in these two patients was 80 and 95 per cent Postoperatively the artery was completely occluded in both cases In one additional patient the preoperative films showed the lumen of the left circumflex branch reduced to 60 per cent and that of the right coronary artery reduced to 90 per cent Postoperative angiograms demonstrated that both vessels were completely occluded but in this patient the status of the graft could not be determined

Discussion

The coronary artery bypass graft (CABG) is currently a commonly performed procedure [1] Much of the information which has been reported has come from a relatively limited number of institutions where the operation has been developed and most of the experience obtained In attempting to assess the future role of the operation it appears desirable to obtain as broad a base of information as possible This would not only be of value in accumulating the surgical results, but would also assist in evaluating the possible extension of the operation to the community hospital

The patients referred to in this report were cared for in a 365 bed private community hospital Surgery was performed by two different groups of surgeons Each surgical team has been doing a wide variety of cardiovascular and open heart surgery in this hospital for the past seven years

The number of patients in this report is relatively small in absolute terms The patients however were drawn from a population receiving medical care at the community level and were all seen in consultations by the author during their hospitalization The series represents therefore a significant segment of the practice of the individual physician caring for cardiac patients

A total of 55 patients underwent CABG The hospital mortality rate was 20 per cent Table I compares the group who survived with the group who did not There was a heavy predominance of men in each group The survivors had an average age ten years less than that of the nonsurvivors The average clinical class was not statistically different for the nonsurvivors compared to the survivors

A history of cardiac failure was much more frequent in those who did not survive

Renal abnormalities discovered by routine postangiography abdominal films

Arturo Meneses Major MC
Richard J McCarty Lieutenant Colonel MC
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El Paso Texas

In 1955 Richards and associates[1] reported on the greater incidence of congenital genitourinary anomalies in patients with congenital heart disease In view of this Abrams and Kaplan[2] pointed out that a film of the abdomen should be obtained 10 to 15 minutes after the injection of contrast media in all cases of congenital heart disease subjected to angiocardiography [2] The excellent urographic study thus obtained frequently demonstrates anomalies of the urinary tract

Yet despite the 10% incidence of some renal or ureteral anomaly found at autopsy in the general population [3] to our knowledge it has not been routine practice by everyone to obtain abdominal films post angiography in adult patients being evaluated for acquired heart disease It is therefore our feeling that this point merits re emphasis In fifty six consecutive cases of patients having either pulmonary or coronary angiography three cases were discovered to have significant renal pathology on postangiography abdominal films and are the subject of this report

Case reports

Case 1 K S was a 38 year old man who had a several year history of exertional chest pain Slight hypertension (140/90) was noted on physical examination which was otherwise normal Laboratory data revealed a Type IV hyperlipoproteinemia ECG and stress tests were normal Coronary angiography revealed 50 to 75 per cent occlusion of three vessels His postangiographic abdominal flat plate showed changes consistent with either unilateral intrarenal hydronephrosis or chronic pyelonephritis (Fig 1)

Case 2 C M was a 30 year old woman who was admitted with sudden pleuritic chest pain and shortness of breath She was taking oral contraceptives for birth control Physical examination revealed an accentuated pulmonic component to the second heart sound Lung scan with ventilation perfusion studies suggested a right lower lobe defect and pulmonary angiography confirmed occlusive lesions of several right pulmonary artery branches A postangiographic abdominal film (Fig 2) revealed clubbing of the superior calyx with loss of architecture suggesting focal pyelonephritis Tuberculous nephritis was subsequently ruled out

Case 3 R F was a 35 year old woman with a two-year history of nonexertional chest pain precipitated by anxiety Physical examination and laboratory data were normal Resting ECG was normal but a prior Master s Test was reported as positive A repeat submaximal treadmill test was negative Coronary angiography was entirely normal The postangiographic abdominal film (Fig 3)

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is no adequate control group with which to compare the figures The desirability and critical need for the availability of a control group in order to allow statistical analysis of treated and untreated groups has been emphasized [4]

The results of this series suggest that there may be important limitations to the CABG procedure The evaluation of the operation as reported has been largely optimistic [5-8] It would appear desirable to have available the results from a cross section of the various institutions now performing this type of surgery, including those at the community level The risks of the procedure in its various settings could then be better gauged and the clinician would gain a more factual overview of the operation

Summary

The early results of 55 patients who underwent the coronary artery bypass graft (CABG) procedure in a large private hospital are reviewed The hospital mortality rate was 20 per cent Excluding death, 55 major complications were found in the total group of patients Fourteen patients had more than one complication Twenty of the 44 surviving patients had no major complication Early postoperative angiograms showed an average graft patency rate of 72 per cent There was some evidence of accelerated closure occurring in a stenotic coronary artery which was grafted From the physician s point of view the patient submitted to the CABG procedure had about two chances out of three of either dying having no patent graft or having a life threatening postoperative complication

The experience with these patients suggests that there may be significant limitations to the performance of this operation or, at least to its possible application in the community hospitals It is hoped that we will acquire a broader base of knowledge about the CABG as it is performed in various institutions across the country

The author gratefully acknowledges the valuable assistance of Mrs Jeanne Heinz R N Cardiology Nurse in the preparation of this report

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Renal abnormalities discovered by routine postangiography abdominal films

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Fig 2 Case No 2 The postangiography abdominal film reveals clubbing of the superior calyx of the right renal pelvis with loss of architecture suggesting focal pyelonephritis.



Fig 3 Case No 3 The postangiography abdominal film demonstrates segmental megaloureter and pelvic distension on the right.

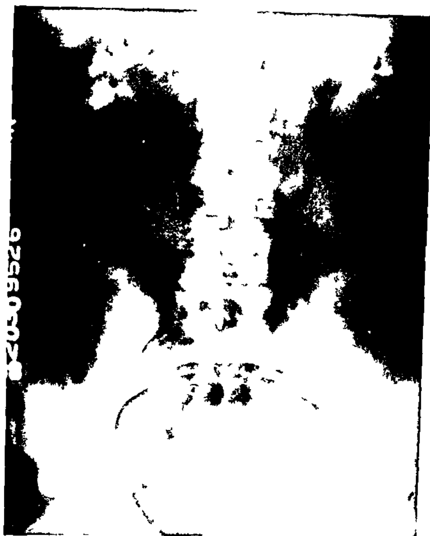


Fig 1 Case No 1 The postangiography abdominal film demonstrates a right renal abnormality suggesting intrarenal hydronephrosis or unilateral chronic pyelonephritis

revealed segmental megaloureter and pelvic distension suggesting a compensated ureteropelvic junction obstruction

Discussion

The high incidence of genitourinary anomalies in the general adult population[3] led us to obtain a routine abdominal film at the termination of the procedure in all patients who had undergone an angiographic study Because high quality films can be obtained this would serve as an excellent screening test in patients with latent genitourinary disease

In fifty six consecutive cases patients had postangiography abdominal films performed and three significant abnormalities were found In one case clubbing of the right upper pole of the calyceal system with loss of architecture suggested focal pyelonephritis Tuberculous nephritis was sought with multiple urine cultures for acid fast bacilli but proved negative In another case the urographic appearance was that of either chronic pyelonephritis or intrarenal hydronephrosis with spontaneous relief of a prior clinically asymptomatic obstruction In the third instance segmental megaloureter and distension of the renal pelvis suggested a compensated ureteropelvic junction obstruction (A fourth case not shown demonstrated indentation of the ureter by an aberrant vessel but was of no clinical consequence)

The results of this study lend support to our recommendation to obtain postangiographic abdominal films in all patients undergoing an angiographic procedure The only risk is the addition of a small amount of radiation exposure which is not felt to be significant when compared to the information obtained

Experimental and laboratory reports

Relation of microcirculatory thrombosis to thrombus in the proximal coronary artery: Effect of aspirin, dipyridamole, and thrombolysis*

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Studies on coronary thrombosis have been traditionally focused on the primary thrombotic obstruction of a major epicardial vessel and the factors favoring its pathogenesis. While results derived from such studies remain of critical importance to the understanding of the determinants favoring the occurrence of coronary occlusion, other aspects of this process have received little or no attention. Sporadic observations made at autopsy have described the presence of thrombi or platelet aggregates in the intramyocardial vessels, posing the question of their potential pathogenetic role in patients with coronary artery disease[1,2] or the dysfunction of other organ.[3-5] However, the role of platelet aggregates in the small vessels distal to a thrombus in a major artery has received little consideration. Conceivably, obstruction of myocardial microcirculation could compromise effective collateral flow and thus intensify the effects of ischemia upon the myocardial area affected by proximal coronary occlusion. In previous studies we observed a substantial decline in the platelets of blood sampled sequentially from the coronary sinus during the formation of a thrombus in the coronary artery.[6,7] We felt that the extent of the drop in platelets could not be solely due to thrombus forming in the epicardial coronary vessel. Since platelet aggregation is considered to be the important factor responsible for the initiation and extension of arterial thrombus,[8] a study was designed to determine platelet distribution in the microcirculation of the myocardium after experimental thrombus of a major coronary vessel. In addition, the recent studies suggesting a potential antithrombotic effect of aspirin[9-11] and dipyridamole,[12-14] two of several agents with anti

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*Presented in part at the 44th Meeting of The American Heart Association, Anaheim, California, 1971.

Summary

Patients with acquired heart disease undergoing angiocardiographic procedures had routine postangiographic abdominal films performed In fifty six consecutive cases with clinically unsuspected renal disease three patients were found to have significant abnormalities

The not infrequent finding of clinically unsuspected renal pathology in patients undergoing angiographic procedures during the evaluation of acquired heart disease has led us to the recommendation that all patients have postangiographic abdominal films This represents an inexpensive screening test for renal pathology with no increase in patient risk

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thrombus) after thrombus formation [19] The length of Thrombolysin infusion was two hours for the early thrombus (five dogs) and four hours for the late thrombus (six dogs) Group IV of 17 and Group V of 7 animals were given respectively 600 mg of aspirin and 100 mg of dipyridamole daily for seven days prior to induction of thrombus The animals were killed and autopsy was performed two to four hours after thrombus formation or immediately after spontaneous ventricular fibrillation The heart was excised the location of the thrombus was noted and its weight was determined Multiple tissue samples of comparable weight were taken from the ischemic and nonischemic area of the heart (Fig 1) from all or several dogs of each group for radioactivity counting and histologic examination (Table I) The radioactivity of the tissue was determined in a well type scintillation counter and expressed as counts per minute per Gm of tissue and also as a count ratio of the ischemic to nonischemic area of each dog after the individual readings of each area were averaged Histologic examination of the cardiac tissue was made in multiple sections stained by hematoxylin-eosin and phosphotungsic acid hemotoxylin For statistical evaluation the results of each treated group were compared to the non treated thrombus group The formula for non paired observation was used for evaluation of thrombus weight and radioactivity ratios whereas for the incidence of arrhythmias the chi square formula was applied

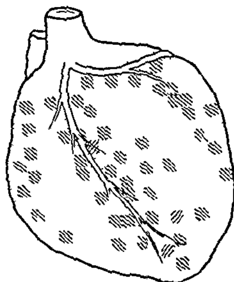


Fig 1 Schematic illustration of distribution of radioactivity in control animals infused with ⁵¹Cr platelet without induction of thrombus The small squares represent the locations from which the tissue samples were taken for radioactivity counting Samples for histology were taken from adjacent areas The shaded part represents schematically the intensity of radioactivity indicating uniform distribution in all segments

Results

A thrombus was formed in 47 out of 56 animals in which it was attempted In Group III lysis of thrombus in the major coronary artery was complete in four and incomplete in three dogs In the remaining four dogs the thrombus did not lyse In Groups IV and V aspirin or dipyridamole failed to affect significantly the incidence or weight of the formed thrombus (Table II) Fig 1 shows schematically the distribution of radioactivity in animals without thrombus production In the three areas from which tissue samples were taken the radioactivity of the labelled platelets was quite comparable at approximately 50 counts per minute per Gm of tissue In contrast following thrombus formation there were distinct areas of radioactivity (Fig 2) Tissue samples from nonobstructed regions presented low activity similar to that found in the no thrombus group An area of high activity was seen in the entire ischemic area distal to the occluding coronary thrombus The counts here obtained from tissue samples of weight comparable to those obtained from nonischemic areas ranged from 130 to 170 per minute per Gm The area adjacent to the main thrombus showed a much higher activity with counts 450 to 600 per minute per Gm of tissue while the thrombus itself showed 5 000 to 13 000 counts per minute per Gm of weight The radioactivity ratio of ischemic to control area when averaging the activity of all samples was 3 3 1 with a range of 2 8 to 9 5 (Table III) The ratio of thrombus radioactivity to that of the control area was 120 average with a range of 60 to 250 On histologic examination the typical findings in all sections from the ischemic myocardial tissue of the nontreated animals

Table I Groups studied

Group	Control no thrombus	Thrombus no treatment	Thrombus + fibrinolysin	Aspirin + thrombus	Persantin + thrombus
	I	II	III	IV	V
Number of animals*	4 (4)	12 (8)	11 (10)	17 (7)	7 (7)

*Numbers in parentheses indicate animals having microcirculatory assessment by histology and radioactivity counts

platelet aggregation properties prompted us to assess their effect, as well as that of thrombolysis upon this preparation

Material and methods

A total of 67 apparently healthy male mongrel dogs fasting for 18 hours and weighing from 19 to 24 kilograms were used They were anesthetized with morphine sulfate (3 mg per kilogram of body weight intramuscularly) and sodium pentobarbital (20 mg per kilogram of body weight intravenously) and subsequently placed on a respiratory pump to maintain adequate ventilation The left jugular vein and left carotid artery were exposed through small skin incisions After an estimate of platelet adequacy in each dog, 170 to 180 ml of blood was taken by means of a polyethelene catheter placed in the jugular vein infusing subsequently equal amounts of isotonic saline to maintain blood volume Platelet rich plasma (PRP) was obtained and the platelet button was then labelled with 300 μc of sodium chromate (^{51}Cr) as described by Aas and Gardner and modified by Aster and Jandle[15] The separation of platelets from canine blood was accomplished by repeated centrifugation of the initial blood sample at speeds ranging from 1 000 to 1 800 r p m for four to seven minutes After obtaining PRP with 75 per cent of the original platelet count as a rule the plasma was centrifuged at high speeds to produce the platelet button After tagging with ^{51}Cr the platelets were infused into the dog and 1 to 1½ hours were allowed for equilibration

At this time production of a platelet coronary thrombus was attempted in 63 dogs by means of a catheter electrode as previously described[6,16] In brief this method employs a No 8 Sones catheter containing a stainless steel insulated wire placed in the anterior descending or circumflex coronary artery By means of a dry cell battery connected to the proximal end of the electrode wire, a 300 to 500 microampere current is applied to the intima of the vessel, resulting in platelet thrombus formation within 15 to 90 minutes Morphologically the thrombus is similar to that described in human arteries[16,18] Its formation in this model is usually indicated by appearance of acute injury potential and multiple premature ventricular beats in the continuously monitored ECG Appearance of injury potential within the first one to two minutes following the placement of the catheter is in our experience, due to mechanical obstruction of the coronary vessel by the catheter Seven such animals were excluded from the study thus leaving a total of 56 dogs with attempted coronary thrombosis The four remaining dogs of the initial group of 67 which received ^{51}Cr tagged platelets had a catheter placed in the coronary artery without attempting induction of thrombosis (Group I) According to the treatment of the animals either before thrombus induction or after thrombus formation the rest of the dogs were divided into various groups (Table I) the no treatment (Group II) comprised 12 animals which received no treatment prior to thrombus induction Eleven animals (Group III) were infused into the left ventricle with Thrombolysin * 2,500 units per kilogram of body weight per hour one hour (early thrombus) or three hours (late

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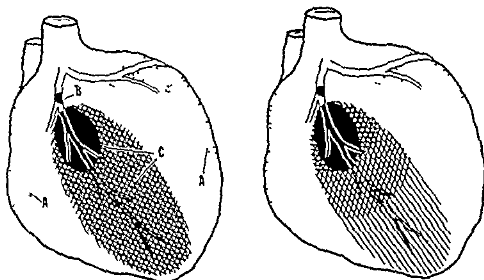


Fig ? *Left panel* Schematic illustration of distinct area of radioactivity following thrombus formation *A* = control area corresponding to nonobstructed coronary artery showing low activity *B* = occluding thrombus *C* = area of high activity which is *more* prominent in the region adjacent to the formed thrombus *Right panel* Distribution of radioactivity in animals pretreated with aspirin and dipyridamole There is a definite decrease in radioactivity becoming minimal *in the distal half of* the ischemic region

they were not included in the table because the animals were given antiarrhythmics This was necessary in order to have two to four hour survivors following thrombus formation which could subsequently be infused with fibrinolysin In this preparation the mortality rate of the animals due to the presence of an obstructing coronary thrombus is approximately 50 per cent within the first two hours and about 90 per cent within four hours following formation of thrombus [20]

Discussion

The results of this study suggest that thrombosis in a major coronary artery is associated at least in the first hours following its occurrence with the presence of platelet thrombi in the microcirculation of the ischemic area The mechanism of formation is not clear Embolization of platelet aggregates from the primary site[1] represents a plausible pathogenetic route Similar mechanisms have been presumed to operate in the microcirculation of other organs such as brain[4] or kidney [5] resulting in damage of the involved tissue Jørgensen and colleagues[2 22] have shown that platelet aggregates induced by adenosin disphosphate infusion into the coronary artery or in the aorta proximal to the renal arteries results in myocardial or renal injury respectively James[1] has suggested that microvascular coronary occlusion by platelet aggregates may play a significant role in the pathogenesis of human myocardial necrosis

In the present study microcirculatory thrombosis was consistently observed in association with major (epicardial) artery thrombosis The role of microvascular thrombosis in the injury produced in ischemic myocardium is open to speculation It is generally agreed that the important factor determining the extent of myocardial damage associated with coronary obstruction is the degree of availability of collateral blood flow The present findings suggest that following proximal obstruction by a thrombus access of available collateral anastomotic flow distally into the ischemic area can be compromised by the presence of multiple platelet aggregates in the intramyocardial vessels although direct evidence for this view is not yet available It

Table II Effect of aspirin and Persantin on major coronary artery thrombosis

Group	*Thrombus no treatment*	*Aspirin + thrombus*	*Persantin + thrombus*
Number of animals	12	17*	7
Weight (mg) of thrombus and SE†	63 ± 20	69 ± 33	114 ± 46

*No thrombus was formed in three animals
†SE = standard error of the mean

Table III Effect of aspirin, dipyridamole, and Thrombolysin on average radioactivity ratios of ischemic to control areas (I/C)

Group	*Control no thrombus*	*Thrombus no treatment*	*Thrombus + Thrombolysin*	*Aspirin + thrombus*	*Persantin + thrombus*
	I	*II*	*III*	*IV*	*V*
Number of animals	4	8	11	7	7
I/C ratio	1 0	3 30	1 84*	1 35*	2 01*

*P < 0 01

was the presence of multiple randomly distributed microthrombi occluding the arterioles and capillaries of the ischemic area These thrombi mainly consisted of platelets and minimal amounts of fibrin (Fig 3) In the area adjacent to the main thrombus a variable degree of thrombus propagation into the side branches could be observed

Pretreatment of the animals with aspirin and dipyridamole or infusion with Thrombolysin, modified the patterns of radioactivity and histology of the microcirculation observed in the nontreated animals (Table III) There was reduced radioactivity in the ischemic area resulting in a significant (P < 0 01) decrease of the ischemic/nonischemic ratio in all treated groups however the distribution pattern of radioactivity varied among Groups III IV and V In the dogs infused with Thrombolysin there was a more or less uniform radioactivity decrease in the entire ischemic region This pattern remained the same whether or not the thrombus was totally, partially or not at all lysed (Table IV) The radioactivity distribution in the animals receiving aspirin or dipyridamole is shown schematically in Fig 2 The main decrease in radioactivity in these animals was observed in the distal half of the ischemic region whereas in the remaining area particularly adjacent to the thrombus the change was smaller Regarding histologic findings in the animals treated with fibrinolysin there was virtually no evidence of microthrombi in sections from the ischemic myocardium However it should be noted that in Groups IV and V disappearance of microthrombi followed a pattern similar to that described above for radioactivity It was observed only in the sections taken from the distal ischemic myocardium whereas in many of the sections taken proximal to the thrombus some degree of microthrombosis was present

There was a decrease in the incidence of arrhythmias and mortality from ventricular fibrillation in the treated animals although it was found significant only for the aspirin group (Table V) The incidence of arrhythmias and mortality in the animals receiving fibrinolysin was also significantly lower when compared to control however

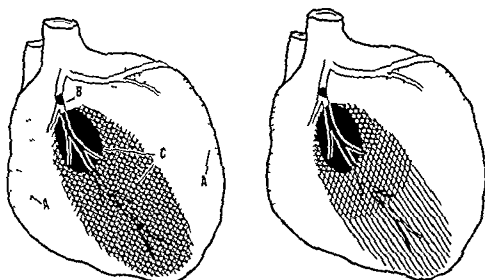


Fig ? Left panel Schematic illustration of distinct areas of radioactivity following thrombus formation *A* — control area corresponding to nonobstructed coronary artery showing low activity *B* = occluding thrombus *C* = area of high activity which is more prominent in the region adjacent to the formed thrombus *Right panel* Distribution of radioactivity in animal pretreated with aspirin and dipyridamole There is a definite decrease in radioactivity becoming minimal in the distal half of the ischemic region

they were not included in the table because the animals were given antiarrhythmics This was necessary in order to have two to four hour survivors following thrombus formation which could subsequently be infused with fibrinolysin In this preparation the mortality rate of the animals due to the presence of an obstructing coronary thrombus is approximately 50 per cent within the first two hours and about 90 per cent within four hours following formation of thrombus[20]

Discussion

The results of this study suggest that thrombosis in a major coronary artery is associated at least in the first hours following its occurrence with the presence of platelet thrombi in the microcirculation of the ischemic area The mechanism of formation is not clear Embolization of platelet aggregates from the primary site represents a plausible pathogenetic route Similar mechanisms have been presumed to operate in the microcirculation of other organs such as brain[4] or kidney[5] resulting in damage of the involved tissue Jørgensen and colleagues[22,23] have shown that platelet aggregates induced by adenosin disphosphate infusion into the coronary artery or in the aorta proximal to the renal arteries results in myocardial or renal injury respectively James[1] has suggested that microvascular coronary occlusion by platelet aggregates may play a significant role in the pathogenesis of human myocardial necrosis

In the present study microcirculatory thrombosis was consistently observed in association with major (epicardial) artery thrombosis The role of microvascular thrombosis in the injury produced in ischemic myocardium is open to speculation It is generally agreed that the important factor determining the extent of myocardial damage associated with coronary obstruction is the degree of availability of collateral blood flow The present finding suggest that following proximal obstruction by a thrombus access of available collateral anastomotic flow distally into the ischemic area can be compromised by the presence of multiple platelet aggregates in the intramyocardial vessels although direct evidence for this view is not yet available It



Fig. 3. Photomicrograph of capillary and arteriol (*left*) with small distended artery (*right*) all occupied by platelet thrombi. (Hematoxylin and eosin. Original magnification ×250.)

Table IV. Effect of lysis of main thrombus on radioactivity ratios of ischemic/control areas

	Thrombus	Thrombus and Thrombolysin		
		Complete lysis	Partial lysis	Occluding thrombus
Number	8	4	3	4
I/C	3.30	1.82	1.89	1.80

was further shown that a relatively short infusion of a thrombolytic agent is capable of minimizing significantly the extent of microcirculatory thrombosis, an effect which was independent of the capability of the thrombolytic agent to dissolve the primary thrombus (Table IV). The same result was obtained following premedication for a relatively brief period with aspirin or persantin which, while failing to affect thrombosis in a major coronary artery as we have demonstrated previously,[18] modified platelet behavior in the microcirculation. Further analysis of these effects would indicate that while platelet aggregation seems to be the primary mechanism responsible for obstruction of the microcirculatory vessels, fibrin, as shown in sections stained with phosphotungstic acid hemotoxylin, appear at some stage of the process, thus explaining the effect of the thrombolytic agent whose action is directed only against fibrin.

On the other hand, the effects of aspirin and dipyridamole, presumably due only to their antiplatelet aggregation properties, should be considered more specific by virtue of their ability to prevent initial platelet aggregation. Regarding their effectiveness at the microcirculatory but not the epicardial vessel level, it should be pointed out that while thrombolytic agents can be variably successful depending on the age of the thrombus,[19] the effectiveness of the aspirin and dipyridamole might be determined by other factors such as size of the vessel[13] or the intensity of the aggregating stimulus in the proximal artery—i.e., electric current. Presumably, the levels of aspirin and dipyridamole in this study were

not adequate to protect against thrombus formation in vessels with diameters much larger than that of the microcirculation Alternatively the favorable results against thromboembolism shown by the studies of Salzman and colleagues[24] and Sullivan and associates[25] suggest that aspirin and dipyridamole are effective only where thromboembolism rather than thrombosis is involved This in turn would indicate that in the pathogenesis of microcirculatory thrombosis embolism is an important mechanism It is recognized that the occurrence of microthrombi in disease states might be determined by other variables which are not necessarily related to the conditions of the model used in this study

Although the significance of microcirculatory thrombosis will have to be further assessed the decrease in incidence of arrhythmias and mortality observed in the groups of animals pretreated with aspirin and dipyridamole is worth emphasizing However only in the aspirin group where the decrease of microcirculatory thrombosis was more impressive (Table III) was it found to be statistically significant (Table V) In this regard it is interesting to note that Haerem[26] found a higher number of intramyocardial arteries occupied by platelet aggregates in patients with known coronary artery disease who died suddenly as compared to those patients who died of noncardiac causes Occlusion of small coronary vessels either supplying directly or responsible for anastomotic access to the various part of the conduction system can potentially cause disturbances of the electrophysiologic function of the heart[1]

Our observations—that fibrinolytic agents aspirin or persantin while failing to affect thrombosis in the major coronary artery modify the platelet behavior in the microcirculation of this model—indicate the necessity for continuing studies in this direction If collateral flow in an obstructed coronary arterial system is the factor of critical importance for electrical stability survival and repair of the ischemic myocardium it is conceivable that such pathology of the microcirculation might be responsible for compromising the effectiveness of this important compensatory mechanism On the other hand metabolic aspects relevant to cardiovascular function

Table V Incidence of arrhythmias and ventricular fibrillation

Group	No of animals	Arrhythmias	Ventricular fibrillation
Control	12	10 (83%)	8 (66 7%)
Aspirin	17	5 (30%)*	2 (12%)*
Persantin	7	3 (43%)†	2 (29%)†

*$P < 0.01$
†P = not significant

should be explored particularly in regard to aspirin whose variable effects upon metabolism have been described[27]

Summary

A study was designed to determine the distribution of platelets in the microcirculation of the myocardium following experimental platelet thrombosis in a major coronary vessel Determination was made by means of ^{51}Cr labelled platelets and histologic examination The results suggest that thrombosis in a major coronary artery is associated at least in the first hours following its occurrence with the presence of platelet thrombi in the microcirculation of the ischemic area Pretreatment with aspirin or dipyridamole minimized significantly the extent of microcirculatory thrombosis without affecting the thrombus in the proximal coronary artery A thrombolytic agent given after thrombus formation had a similar effect upon microcirculatory thrombosis remaining also independent of its effect upon proximal coronary artery thrombosis There was a decrease in incidence of arrhythmias and mortality rate in the group of animals pretreated with aspirin and dipyridamole

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Electrophysiological effects of lidocaine on distal Purkinje fibers of canine heart

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The tertiary amine lidocaine hydrochloride was first noted to have antiarrhythmic effects on the hearts of experimental animals in 1950.[1] Subsequently, it was shown that injections of lidocaine either abolished or markedly attenuated the ventricular premature beats which occurred in patients after myocardial infarction,[2-5] after open heart surgery,[6-8] and in situations of presumed digitalis overdose.[9,10] In 1969 Sugimoto and associates[11] reported certain of the electrophysiological effects of lidocaine on the intact heart and noted marked differences between the effects of lidocaine and either quinidine or procainamide. Davis and Temte[1] noted that in isolated Purkinje fibers lidocaine shortened the duration of the action potential and failed to significantly reduce the maximal rate of rise of phase 0.

In a recent report, Myerburg and colleagues[13] called attention to a marked disparity between the times of repolarization in adjacent distal Purkinje fibers. The long duration of action potentials and refractoriness in some Purkinje fibers could prevent the propagation of premature beats across the segment of distal Purkinje tissue with the longest action potential duration. This segment functioned as a "gate." The gating function of distal Purkinje fibers was ascribed to longer action potentials and their long refractory period was thought to contribute to decremental conduction and block of early premature impulses. Because lidocaine has been shown to shorten action potential duration, this study was undertaken to examine the effects of lidocaine on distal Purkinje fibers and the functional consequences of these effects on the propagation of early premature beats. The results of this study suggest a potentially important mechanism for the antiarrhythmic action of lidocaine and a model system for the study of other antiarrhythmic agents.

Methods

These experiments were performed on isolated cardiac tissues obtained from healthy adult mongrel dogs. The dogs were anesthetized with sodium pentobarbital, 30 mg. per kilogram of body weight given intravenously, and the heart was removed

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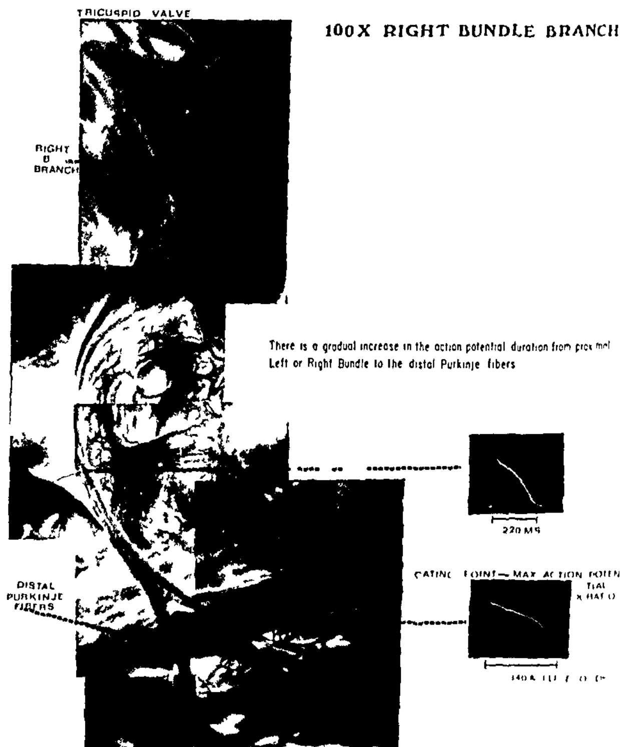


Fig 1 Photograph of the preparations used in these studies The photo is of the right septal surface The septal leaflet of the tricuspid valve is above The anterior papillary muscle projects to the left in the center of the photo The right bundle branch and free running distal Purkinje fibers have been stained dark with Lugolo solution Typical action potentials from the proximal right bundle branch and distal Purkinje fibers are shown in the inserts

through a right thoracotomy Longitudinal cuts were made parallel to the ventricular septum, one along the anterior interventricular groove and one along the posterior groove The chordae tendeneae were then cut at their attachment to the tricuspid valve and the right ventricular free wall was reflected away from the septum The right bundle branch was identified at the level of the membranous septum and was transected at this level A layer of septal muscle, 3 to 5 mm in thickness and containing

the right bundle branch was dissected and removed At the base of the anterior papil lary muscle the right bundle branch became a free running strand with two or more branches which inserted into the endo cardial surface of the right ventricular free wall A section of the free wall containing these insertions also was removed The preparation thus included (1) the proximal right bundle branch (2) the anterior papil lary muscle (3) the false tendon(s) and (4) an endocardial section of the right ven tricle to which the false tendons inserted (see Fig 1) After transferring this prepa ration to a tissue bath the muscle between the anterior papillary muscle and the right ventricular wall was divided so that the false tendon(s) was the only connection between the right bundle branch and the right ventricular wall The tissue was then fixed to the silastic bottom of the bath with small stainless steel pins and perfused at a rate of 10 ml per minute with a modified Tyrode solution which was equilibrated with 95 per cent oxygen and 5 per cent carbon dioxide The Tyrode solution was composed of the following (mM concen tration) NaCl 137 $NaHCO_3$ 12 $CaCl_2$ 2 2 KCl 5 4 $MgCl_2$ 0 5 NaH_2PO_4 1 8 and dextrose 5 5 Temperature within the bath was maintained at 38 ± 0 5° C by an electrofilm heating element beneath the silver bath The film was powered by a fully rectified direct current source and was regulated by a thermocouple within the bath and a feedback control circuit

Transmembrane action potentials were recorded with glass microelectrodes The microelectrodes were machine pulled with a Kopf vertical pipette puller and filled by boiling in 3 M KCl under reduced atmos pheric pressure The tip resistance of the electrodes was between 10 and 30 Meg ohms The microelectrode were connected through an Ag AgCl bridge to Bioelectric Instruments MHI holders and to the input of a unity gain voltage follower with an input impedance of $>10^{11}$ ohms The out puts from these preamplifiers were dis played on a Tektronix 564 storage oscillo scope Photographs were taken with a C 12 Polaroid camera The preparation was stimulated through a bipolar extracellular electrode insulated with Teflon except at its tip Stimulating pulses were derived from a Grass Model S 4 pulse generator and isolation unit The pulse generator was triggered by a series of Tektronix 161 pulse generators This system provided pulses at any desired basic driving frequency and a dividing circuit between two pulse gener ators permitted the delivery of premature test pulses after every sixth basic pulse at any desired coupling interval The pulses were 3 msec in duration and adjusted to two times threshold

In each experiment two simultaneous action potentials were recorded Initially while pacing the preparation from the prox imal right bundle branch one microelec trode was moved in 1 to 2 mm steps from the proximal right bundle out along a false tendon and distal Purkinje fibers up to the point where they penetrated the endo cardial surface of the right ventricular free wall At each position action potential dura tion was recorded After determining the area of maximal action potential duration one microelectrode was positioned approxi mately 1 cm proximal to that area and a second microelectrode was placed 2 to 3 mm distal to the area Propagation of pre mature test pulses was then examined Finally, normal Tyrode solution was sub stituted with Tyrode solution containing lidocaine hydrochloride in concentrations from 1×10^{-8} to 1×10^{-4}M

Definitions

1 Action potential duration (APD) The interval between the upstroke of the action potential (phase 0) and 80 per cent re polarization

2 Gating point The site in the false ten don at which maximal action potential duration was observed

3 Functional refractory period of the gate (FRPG) The minimal interval between the upstrokes of action potentials distal to the gating point in response to a premature stimulus delivered proximal to the date

Results

The effect of lidocaine on the time course of repolarization in Purkinje fibers was examined in 10 preparations The results of these studies are presented in Fig 2 In each study the preparation was driven at a frequency of 60 beats per minute (i e cycle length 1 000 msec) and transmem

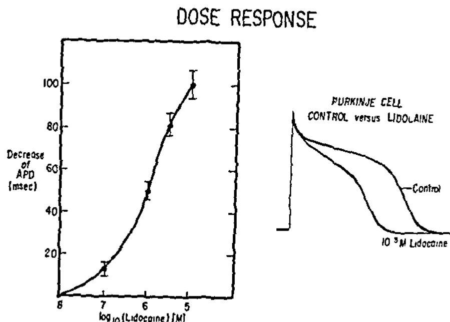


Fig 2 Effects of lidocaine on action potential (*right panel*) and dose-response curve (*left panel*) *APD* = action potential duration

brane action potentials were recorded from Purkinje fibers in the free running strand approximately 1 cm from its insertion into the subendocardium of the right ventricle Lidocaine produced a dose dependent decrease of action potential duration A typical transmembrane action potential obtained before and after exposure to lidocaine is shown in the right panel of Fig 2 The relation between the concentration of lidocaine and the decrease of action potential duration is shown in the left panel of Fig 2 At 1×10^{-8}M lidocaine produced no change of action potential duration At 1×10^{-7}M lidocaine decreased action potential duration by 13 3 ± 1 5 msec At 1×10^{-6} and 5×10^{-6}M lidocaine decreased action potential duration by 50 ± 4 5 and 81 ± 5 0 msec respectively At a concentration of 1×10^{-5}M lidocaine decreased action potential duration by 100 ± 6 7 msec and no further decrease was noted at 5×10^{-5}M Previous work by Bigger and Heissenbuttel[4] and by Gianelly and colleagues[5] has indicated that the therapeutic concentration of lidocaine in plasma is approximately 2 5 μg per milliliter Lidocaine 1×10^{-5}M corresponds to a concentration of 2 34 μg per milliliter

Under control conditions the duration of action potentials recorded from Purkinje fibers along the right bundle branch varies [13] As cells were impaled sequentially in the proximal right bundle branch false tendon, and terminations of the Purkinje system at the endocardial surface of the right ventricle action potential duration increased and then decreased The region of maximal action potential duration was located within the false tendon and was usually 2 to 5 mm proximal to the site where a free running strand penetrated the endocardial surface A representative map of action potential durations along the right bundle branch and false tendon before and after exposure to lidocaine is shown in Fig 3 Under control conditions action potential duration increased from 225 msec in the proximal right bundle branch to 240 msec at the level of the anterior papillary muscle As the right bundle branch became a free running strand action potential duration increased to a maximum of 305 msec and then decreased rapidly to 200 msec just before the strand penetrated the endocardium of the right ventricular free wall The preparation was then perfused with Tyrode solution which contained $1\ 5 \times 10^{-5}$M lidocaine The steady state maximal effects of lidocaine were achieved in 7 to 8 minutes Twenty minutes after exposure to lidocaine the map of action potential duration over the conducting system was repeated Action potential duration was decreased by lidocaine throughout the preparation, but the maxima ect was

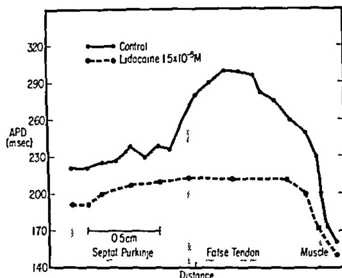


Fig 3 Map of action potential durations in the right bundle branch false tendon and ventricular muscle (see Fig 1) Solid circles show *APD* before perfusion with lidocaine Dashed curve shows *APD* after exposure to lidocaine Note that lidocaine shortened *APD* maximally in the false tendon

Table I Effects of lidocaine (1×10⁻⁵ M) on action potential duration (msec)

Experiment no	Proximal RBB		Mid RBB		Gate		Distal		Ventricular muscle	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	225	220	290	225	300	220	235	200	180	175
2	205	200	265	210	330	210	250	210	150	145
3	210	215	260	220	320	220	230	198	160	155
4	220	210	260	227	295	235	240	220	143	134
5	235	215	265	220	310	220	240	200	155	150
6	225	200	240	210	305	210	235	200	170	160
7	215	195	240	195	320	195	260	190	180	175
8	210	200	260	210	305	210	240	210	160	150
9	220	205	240	205	330	200	250	200	180	195
10	230	200	250	205	305	200	250	200	175	168
Average change	13.5 ± 3.3		47.8 ± 4.4		100.0 ± 6.7		40.2 ± 4.4		6.6 ± 0.8	
P value	P > 0.001		P > 0.001		P > 0.001		P > 0.001		P > 0.001	

noted at the region of maximal action potential duration Thus in the proximal right bundle branch action potential duration was decreased from 225 to 200 msec while in the free running strand action potential duration decreased from 290 to 205 msec In the most distal Purkinje fibers where action potential duration was already short the effects of lidocaine were small relative to the free running strand The effects of lidocaine on the duration of action potentials in 10 preparations are summarized in Table I Lidocaine decreased action potential duration in the proximal right bundle branch by an average of 13 msec at the base of the papillary muscle by 47 msec at the area of maximum action potential duration by 100 msec and at distal fibers by 40 msec Lidocaine decreased action potential duration of ventricular muscle by only 6 msec Thus the most prominent effect of lidocaine was to shorten action potential duration at the region of maximal duration during the control period

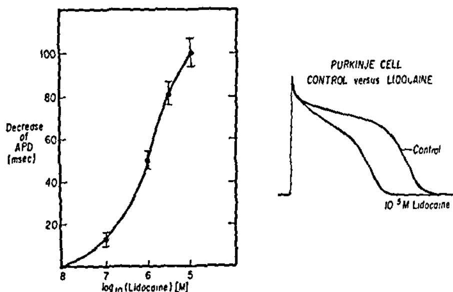


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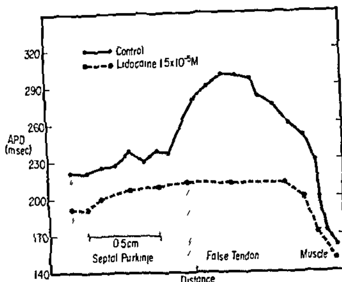


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Table I Effects of lidocaine (1×10^{-5} M) on action potential duration (msec)

Experiment no	Proximal RBB		Mid RBB		Gate		Distal		Ventricular muscle	
	Before	After	Before	After	Before	After	Before	After	Before	After
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2	205	200	265	210	330	210	250	210	150	145
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4	220	210	260	222	295	235	240	220	143	134
5	235	215	265	220	310	220	240	200	155	150
6	225	200	240	210	305	210	235	200	170	160
7	215	195	270	195	320	195	260	190	180	175
8	210	200	260	210	305	210	240	210	160	150
9	220	205	240	205	330	200	250	200	180	195
10	230	200	250	205	305	200	250	200	175	168
Average change	13.5 ± 3.3		47.8 ± 4.4		100.0 ± 6.7		40.2 ± 4.4		6.6 ± 0.8	
P value	P > 0.001		P > 0.001		P > 0.001		P > 0.001		P > 0.001	

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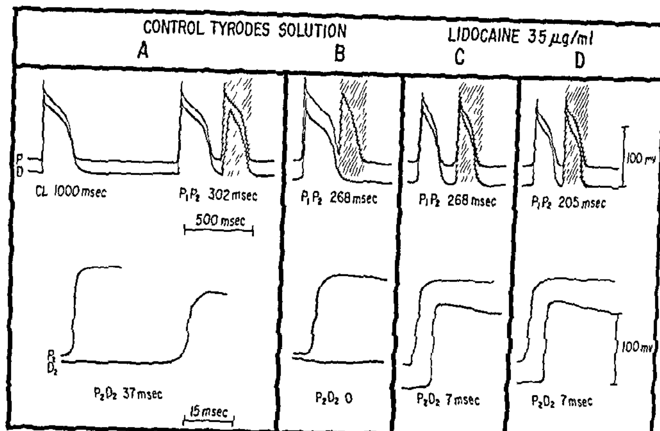


Fig 4 *A through D* Effects of lidocaine on *APD* and propagation of early premature beats *P* = cell proximal to the gate *D* = cell distal to the gate Lower tracings show expanded time sweep to illustrate dv/dt of the upstroke and P_2-D_2 interval *Panels A* and *B* are before lidocaine *Panels C* and *D* are after exposure to lidocaine See text for details

As a consequence of this effect action potential durations became more uniform in the Purkinje strand and the marked discrepancy of action potential durations which normally exists between the free running strand and the adjacent muscle was largely abolished

Myerburg and colleagues[13] described the gradual increase of action potential duration in distal Purkinje fibers and noted that the area of maximal duration functioned as a "gate Premature stimuli delivered either to the proximal right bundle branch or to distal ventricular muscle were blocked at the gate when the coupling interval was less than action potential duration at the gate Fig 4 *(panels A and B)* illustrates this phenomenon In panel *A* action potentials were recorded simultaneously from cells proximal and distal to the area of maximal action potential duration After a series of beats at a basic cycle length of 1 000 msec a premature stimulus was introduced into the right bundle branch In the proximal cell the premature response occurred 302 msec after the last basic response and propagated across the gate to the distal cell The interval between the proximal and distal response on the premature beat was 37 msec At a coupling interval of 301 msec the premature pulse elicited a response in the proximal cell, but this response failed to propagate across the gate A premature test pulse still elicited a response in the proximal cell at coupling intervals as short as 268 msec *(panel B)* The effects of lidocaine are shown in panels *C* and *D* After lidocaine action potential duration was reduced At a coupling interval of 268 msec (the same as panel *B*) a premature test pulse elicited a response in the proximal cell which propagated across the gate The interval between the proximal and distal responses on the premature beat was only 7 msec *(panel C)* After exposure to lidocaine the coupling interval between the basic and premature beat could be further reduced to 205 msec while propagation across the gate was maintained *(panel D)* Not only was propagation across the gate

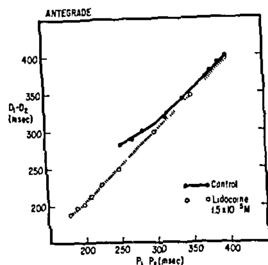


Fig 5 Effects of lidocaine on the functional refractory period of the gate (*antegrade*) P_1P_2 = interval between basic and premature responses proximal to gate D_1D_2 = corresponding intervals distal to the gate *Antegrade* = propagation from right bundle to right ventricle Basic cycle length = 1 000 msec

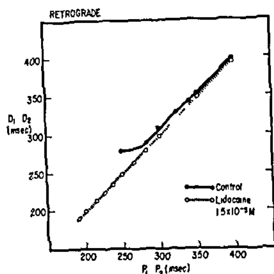


Fig 6 Effects of lidocaine on the functional refractory period of the gate (*retrograde*) Nomenclature the same as Fig 5 *Retrograde* = propagation from right ventricle to right bundle branch Basic cycle length = 1 000 msec

maintained but the decremental conduction and delay which was evident in panel *A* was absent after lidocaine (*panels C* and *D*) Results comparable to these were observed in each of 10 preparations

The effects of lidocaine on propagation across the gate are further depicted in Figs 5 and 6 In Fig 5 action potentials were recorded proximal and distal to the gate while driving the preparation from the right bundle branch (antegrade) Premature test pulses were delivered to the right bundle at progressively shorter coupling intervals and the interval between action potentials in the proximal cell (P_1 P_2) was plotted against the corresponding interval between action potentials in the distal cell (D_1 D_2) During the control period the D_1 D_2 interval began to increase at P_1 P_2 intervals of approximately 300 msec (i e delayed propagation of the premature response) At a P_1 P_2 interval of 250 msec the premature beat failed to propagate across the gate The shortest interval between responses in the distal cell (i e 270 msec in Fig 5) defined the functional refractory period of the gate After lidocaine the functional refractory period of the gate was reduced to 190 msec Decremental conduction of early premature beats which was evident before lidocaine was abolished

In Fig 6 the same type of plot was used to depict the effects of lidocaine on retrograde conduction across the gate In this instance the preparation was driven from the right ventricular free wall so that the impulse propagated retrograde across the free running strand to the right bundle branch Action potentials were recorded proximal (near ventricular muscle) and distal (near the right bundle branch) to the area of maximal action potential duration Before lidocaine the functional refractory period of the gate was 275 msec and premature beats with short coupling intervals were propagated with decremental conduction After lidocaine the functional refractory period was reduced to 190 msec and decremental conduction was abolished

Discussion

In 1969 our group reported certain of the electrophysiologic effects of lidocaine on the heart in awake dogs [11] Lidocaine decreased the ventricular rate of dogs with chronic heart block and produced a substantial increase in the threshold for stimulation of atrial and ventricular muscle Somewhat to our surprise lidocaine failed

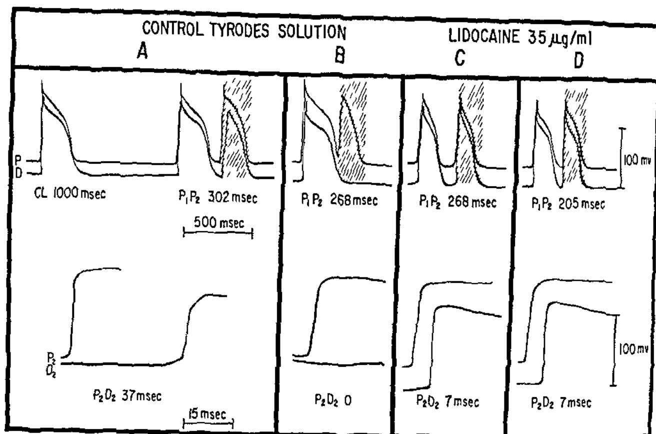


Fig 4 *A through D* Effects of lidocaine on *APD* and propagation of early premature beats P = cell proximal to the gate *D* = cell distal to the gate Lower tracings show expanded time sweep to illustrate dv/dt of the upstroke and P_2-D_2 interval *Panels A* and *B* are before lidocaine *Panels C* and *D* are after exposure to lidocaine See text for details

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Myerburg and colleagues[13] described the gradual increase of action potential duration in distal Purkinje fibers and noted that the area of maximal duration functioned as a ' gate Premature stimuli delivered either to the proximal right bundle branch or to distal ventricular muscle were blocked at the gate when the coupling interval was less than action potential duration at the gate Fig 4 *(panels A* and *B)* illustrates this phenomenon In panel *A* action potentials were recorded simultaneously from cells proximal and distal to the area of maximal action potential duration After a series of beats at a basic cycle length of 1 000 msec a premature stimulus was introduced into the right bundle branch In the proximal cell the premature response occurred 302 msec after the last basic response and propagated across the gate to the distal cell The interval between the proximal and distal response on the premature beat was 37 msec At a coupling interval of 301 msec the premature pulse elicited a response in the proximal cell but this response failed to propagate across the gate A premature test pulse still elicited a response in the proximal cell at coupling intervals as short as 268 msec *(panel B)* The effects of lidocaine are shown in panels *C* and *D* After lidocaine action potential duration was reduced At a coupling interval of 268 msec (the same as panel *B)* a premature test pulse elicited a response in the proximal cell which propagated across the gate The interval between the proximal and distal responses on the premature beat was only 7 msec *(panel C)* After exposure to lidocaine the coupling interval between the basic and premature beat could be further reduced to 205 msec while propagation across the gate was maintained *(panel D)* Not only was propagation across the gate

maximal in distal Purkinje fibers at the region of the gate The effect of lidocaine on proximal Purkinje fibers within the right bundle branch and on ventricular muscle is much less marked Thus one consequence of the action of lidocaine is to diminish nonuniform repolarization in distal Purkinje fibers and to reduce the discrepancy of action potential durations which normally exists between Purkinje fibers and ventricular muscle A second consequence of this action is to abolish or markedly attenuate the gating function of the distal Purkinje fibers An important result of these actions is to shorten the functional refractory period of the gate and to abolish decremental conduction of premature impulses which arrive at the gating segment early in its phase of recovery of excitability Our studies indicate that these actions of lidocaine on the gating segment of Purkinje tissue are applicable whether the premature impulse invades the gate from above (i e antegrade) or from below (i e retrograde)

In considering the potential significance of our data to the intact heart at least three pieces of additional data would be desirable First it remains to be proved that lidocaine exerts the above actions on the Purkinje system of the intact awake animal or man Second it would be very desirable to know if lidocaine exerts a quantitatively similar effect on all gating segments since as noted by Myerburg and colleagues[13] nonuniformity of gates whether spontaneous or pharmacologically induced could enhance the likelihood of arrhythmias rather than the protective effect we have attributed to the actions of lidocaine Finally it would be of particular interest to induce re entrant beating at the Purkinje muscle junction by interventions which are analogous to those which may operate in disease and to examine the influence of lidocaine under these conditions

For the reasons noted above it is premature to ascribe the antiarrhythmic actions of lidocaine to its effect on distal Purkinje fibers and the gating function of that segment of the Purkinje muscle junction The marked discrepancies of action potential duration which normally exist in this region however as well as the proximity of this segment to areas of disease—i e intramural infarcts—and the apparent sensitivity of the gating segment to pharmacological agents all make this a particularly attractive model system for the evaluation of antiarrhythmic drugs

Summary

These studies were designed to examine the electrophysiological effects of lidocaine on distal Purkinje fibers of the canine heart Standard microelectrode techniques were used to record transmembrane action potentials from the right bundle branch free running strands of Purkinje tissue, and ventricular muscle The duration of action potentials was maximal in the distal Purkinje fibers The long duration of action potentials in these distal fibers determined the functional refractory period of the Purkinje muscle junction Early premature beats initiated on either side of the distal Purkinje fibers propagated with decrement or were blocked Lidocaine shortened the action potential of Purkinje fibers but had little effect on muscle The effect of lidocaine on action potential duration was dose dependent and was maximal in these distal Purkinje fibers As a consequence of its ability to shorten action potential duration lidocaine reduced the degree of nonuniformity of recovery of excitability Lidocaine shortened the functional refractory period of distal Purkinje fibers and abolished decremental conduction of early premature beats These effects may contribute to the antiarrhythmic actions of lidocaine

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to produce significant alterations of conduction velocity in Purkinje tissue total ventricular activation time or refractoriness of ventricular muscle Lidocaine thus appeared to have very different electrophysiological properties than quinidine[14] At the time of our earlier report there were no published data concerning the effects of lidocaine on the action potential of cardiac fibers

In 1969 Davis and Temte[1] described the effects of lidocaine on isolated Purkinje fibers and ventricular muscle At concentrations from 5 to 50 μg per milliliter the most prominent effect of lidocaine was an acceleration of repolarization which resulted from an increase in the slope of phase 2 and an earlier onset of phase 3 This effect of lidocaine was confined to the Purkinje fibers however and little change in the duration of action potentials was noted in ventricular muscle These investigators[1] also observed that lidocaine abolished decremental conduction across the distal Purkinje fibers when premature stimuli were delivered to the preparation during the early phase of recovery of excitability

In 1970 Bigger and Mandel[15] reported that lidocaine in concentrations of 1×10^{-6} and 1×10^{-5} attenuated on abolished spontaneous phase 4 diastolic depolarization in Purkinje fibers and shortened action potential duration Lidocaine had little or no effect on the maximal rate of phase 0 depolarization Bigger and Mandel[15] postulated that the effect of lidocaine on phase 4 diastolic depolarization and on the duration of the action potential could be attributed to an increase of membrane conductance for potassium

In 1971, Singh and Vaughan Williams[16] confirmed the observations of Davis and Temte[1] and Bigger and Mandel[15] with respect to the effect of lidocaine on action potential duration They also indicated that lidocaine decreased max dv/dt of the upstroke of cardiac muscle They considered that the failure of Bigger and Mandel[15] to observe this latter effect might have been accounted for by a relatively low K^+ concentration in their Tyrode solution Most investigators now agree however that an important and consistent effect of lidocaine is to decrease action potential duration that this effect is more prominent in Purkinje fibers than in ventricular muscle and that at therapeutic concentrations lidocaine has only a slight depressant effect on conduction velocity

Moe and Han and their colleagues[17,18] have stressed the potential importance of nonuniform recovery of excitability in adjacent regions of myocardium to the genesis of re entrant arrhythmias In the above reports these investigators have shown that the 'vulnerable period' corresponds to an interval of nonhomogenous recovery of excitability in the myocardium and that agents which either increase or decrease the degree of nonhomogenous recovery respectively make the heart more or less vulnerable to fibrillation induced by a premature stimulus The data which led to that conclusion were based on measurements of the refractory period at adjacent areas of epicardial muscle, and discrepancies in the range of 10 to 20 msec In the report by Myerburg and colleagues[13] the duration of the action potential and refractory period of distal Purkinje fibers was noted to be 80 to 100 msec longer than in adjacent muscle Myerburg and colleagues[13] attributed a protective effect to the gating segment of distal Purkinje fibers but considered the possibility that should a localized breakdown of the gate occur during ischemia for example that this could create certain of the conditions necessary to support a re entry circuit Previous experiments by Alanis and co workers[20] had demonstrated slow conduction and unidirectional block at the Purkinje muscle junction The observations by Moe and colleagues[17,19] Myerburg and associates[13] and Alanis and co workers[20] suggested to us that the marked differences of action potential duration at the Purkinje muscle junction might contribute to arrhythmias of the vulnerable period and that distal Purkinje fibers might be a particularly rewarding site to examine the effects of lidocaine

Our studies have shown that lidocaine in concentrations which are equivalent to therapeutic levels in plasma of man exerts a prominent effect on the duration of action potentials in Purkinje fibers The ability of lidocaine to shorten action potential duration is dose dependent and the effect is

Activation of the human fetal heart

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Recent attempts to correlate electrical activity of the heart to the surface electrical field[1,2] and the new data on disturbances of impulse transmission in the ventricles[3] have aroused a new interest in cardiac activation

Our present knowledge of the excitation process of the heart is based mainly on animal experiments[4-9] Some data also have been gathered in humans[10-12] mostly from studies performed during cardiac surgery[13-20] These studies although useful have obvious technical limitations The work of Durrer and his group[21-23] on the perfused human heart is an important exception these workers have also demonstrated that as far as cardiac excitation is concerned the electrical behavior of the isolated and perfused heart is practically identical to the one of the heart in vivo

This paper deals with a study of the activation process of the human fetal heart

Material and methods

The present study was carried out on 11 human fetal hearts removed within 30 minutes after death which were revived and perfused with the Langendorf technique The age of the fetuses varied from 5½ to 9 months In each case a routine ECG was taken shortly before death and was found to be normal[24] At the end of each experiment the heart was carefully examined and was found to be free from any gross structural abnormality Perfusion was performed with a modified Tyrode solution *

By means of surface and multipolar needle electrodes with an interterminal distance of 0 5 mm bipolar records were obtained from the epicardium left and right endocardium and from the septal wall An eight channel Electronics for Medicine apparatus was used with an electronic switch at a paper speed of 200 mm per second Magnification of the tracings with magnifying lens allowed measurement of activation times with an accuracy of 1 msec An average of 300 points were explored in each heart (of these between 50 and 60 were on the atria) A reference lead was recorded with one electrode placed at the apex and the other at the root of the aorta The left endocardium was exposed through a longitudinal cut along the obtuse margin of the heart Similarly the right ventricular cavity was opened with a cut along the acute margin The results were discarded if any changes in the form and duration of the QRS occurred in the reference lead which was carefully monitored during the experimental procedure For atrial activation the beginning of the P wave served as a time reference for ven

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Tyrod olutio = NaCl 137 mm KCl 2 7 mm $CaCl_2$ 2 7 mm N HCO_3 12 mm N H PO 1 8 mm $MgCl_2$ 0 5 mm. and gl cose 5 5 mm

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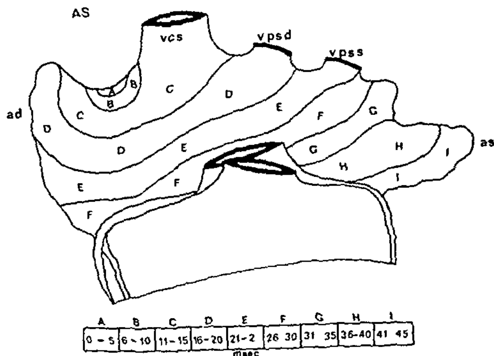


Fig 2 Same heart as in Fig 1 *AS* = antero superior aspect of the atria *ad* = right atrium *as* = left atrium *vcs* = superior vena cava *vpsd* = right superior pulmonary vein *vpss* = left superior pulmonary vein

several exceptions In some instances the latest activity occurs on the posterior lateral portion of the left ventricle while excitation of the subpulmonic area occurs relatively early Furthermore in the case presented in Fig 3C a small area of very early activation is present on the posterior aspect of the right ventricle and another area of early activity is observed on the upper anterior portion of the left ventricle near the AV groove

Altogether epicardial activation when a sufficient number of points are explored seems to be a phenomenon which is highly complex and extremely variable from one normal heart to the other

This observation cast some doubts on the reliability of predicting the details of epicardial and ventricular excitation from mapping of surface potential differences Similar observations have been previously reported by King and colleagues[25] for atrial activation

Within the ventricles three regions of very early activity are found (Fig 4A) all of them on the left endocardial surface The first one is located on the central portion of the middle third of the septum the second area is high on the parietal endocardium close to the anterior AV groove and the third one again on the parietal endocardium is located near the mid lower portion of the left posterior paraseptal region These findings are in complete agreement with those obtained by Durrer and associates[3] in adult human hearts The three areas mentioned above might well represent the functional trifurcation of the left main bundle

From these initial foci activity spreads quickly in the next 5 msec to most of the left parietal and septal endocardium The anterior apical and basal septal zones are the last activated regions Excitation on the left endocardium seems to be a rather uniform and quick event which is completed within 20 msec from the beginning of the QRS complex

In the right ventricular endocardium (Fig 4B) activity occurs first in just one area on the parietal wall near the base of the anterior right papillary muscle 15 msec after the beginning of QRS From this region activity spreads slowly along

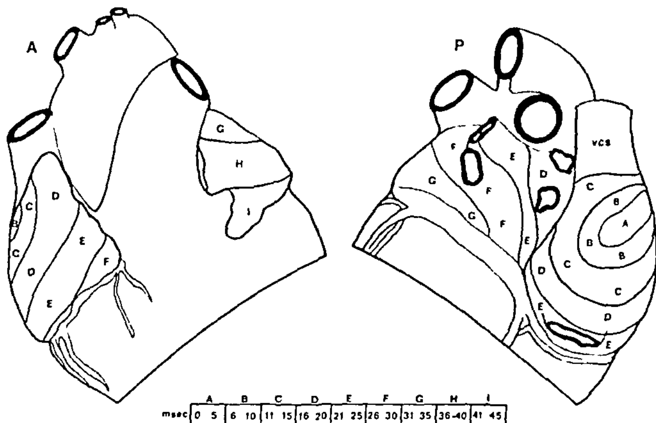


Fig *1* Activation of the atria (Age of subject 6½ months weight of heart 4 8 grams) *A* = anterior view *P* = posterior view *VCS* = superior vena cava Activation times are given in msec after the beginning of the P wave in the reference lead

tricular activation the beginning of QRS was taken as time zero

Results and discussion

Activation of the atria begins in the region of the sinus node as an irregular oval area, within 0 and 5 msec from the beginning of the P wave in the control lead From this area excitation spreads radially following a series of concentric equal isochrones Each isochrone involves simultaneously both a posterior and a supero anterior portion of the atrial wall As shown in Figs *1* and *2* the activation front proceeds in a cranio caudal direction and from right to left In four cases no electrical activity could be registered on the posterior aspect of the left atrium in the region of the pulmonic veins The width of the isochrones is equal in each region of the atria suggesting a rather uniform velocity of conduction This finding and the general pattern of atrial activation would tend to exclude the existence of specialized atrial pathways along which activity spreads preferentially from right to left atrium Consequently it should be pointed out that the idea of functional specialized interatrial tracts is based mainly on indirect deductions in animal experiments [5] by the difference in shape of intracellular action potentials [26] and from the sensitivity of atrial cells to changes in external potassium concentration [27] However since the atrial septum was not explored in our studies the existence of possible internodal preferential tracts can not be ruled out

Epicardial activation of the ventricles begins as a rule in a small area on the trabecular wall of the right ventricle (Fig *3A*) it then proceeds to the anterior and posterior paraseptal regions Sometimes as in the case shown in Fig *3B* this second area of early activation involves the apical region as well Epicardial breakthrough subsequently occurs in an apico basal direction involving large portions of the free ventricular wall The last activated regions are the diaphragmatic and basal portions of the right ventricle However there are

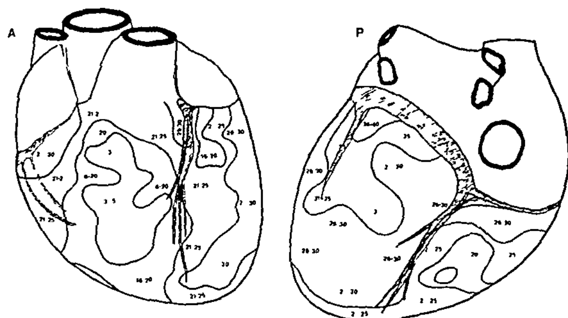


Fig 3C Epicardial activation of the ventricles of a fetal human heart (Age of subject 7 months heart weight 6 grams) Abbreviations as in *3A* Note the early activity on the posterior aspect of the right ventricle and on the anterior part of the left ventricle near the AV sulcus

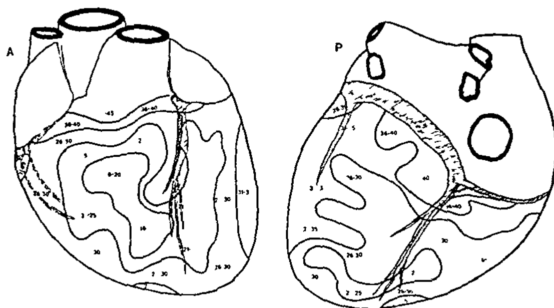


Fig *3D* Epicardial activation of the ventricles of a fetal human heart (Age of subject 6½ months heart weight 5 5 grams) Abbreviations as in *3A*

Fig 3A Epicardial activation of the ventricles of a fetal human heart (Age of subject 5½ months heart weight 4 grams) *A* = anterior view *P* = posterior view

Fig 3B Epicardial activation of the ventricles of a fetal human heart (Age of subject 6 months heart weight 5 4 grams) Abbreviations as in *3A*

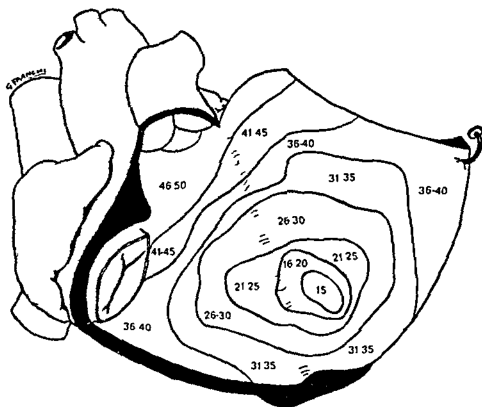


Fig 4B Same heart as illustrated in 4A Activation of the right endocardium

of the septum while the wave of excitation advances mainly tangentially in the apical and basal septal mass Excitation of the septum always occurred from left to right right to left penetration as described in dogs[29] *and in adult human hearts* [27] was never observed

Summary

Epicardial activation of atria and ventricles endocardial activation of the ventricles and intramural activation of the interventricular septum were studied in 11 isolated revived and perfused human fetal hearts No evidence was found for specialized pathways in the atria Earliest epicardial breakthrough in the ventricles occurred in the area pretrabecularis of the right ventricle ometimes an early area was found on the posterior aspect of the right ventricle Latest activated areas were the diaphragmatic and basal aspects of the right ventricle on occasion the latest region was the posterolateral part of the left ventricle On the endocardial surface three regions of early activity were found the central part of the middle third of the left part of the septum an area located *near the base of the left anterior free wall* and a region near the middle lower part of the left posterior paraseptal region Septal activation occurred in a left to right direction only nowhere was a right to left spread of excitation found The intramural spread of excitation was perpendicular to the endocardial surface in the central part of the interventricular septum and in the free wall of the left ventricle In the basal and apical parts of the interventricular septum and in the free wall of the right ventricle excitation spreads in a tangential fashion

We would like to thank Prof D Durrer and Dr G Janse from Amsterdam for reviewing the manuscript for their criticism and for their many helpful suggestions

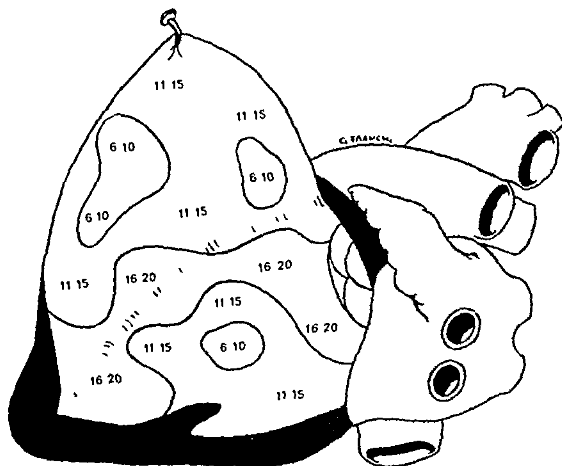


Fig. 4. Endocardial activation of a fetal human heart (subject age 6½ months, heart weight 5.5 grams). Same heart as in Fig. 3A. In this figure an ideal cut has been made along the posterior I-V septum. Here we see activation of the left endocardium.

concentric isochrones toward the periphery of the septal and parietal endocardium, the general direction of activation is from apex toward base and from left to right. The basal endocardium and the septum just below the pulmonic valves are activated last, synchronously with the end of QRS complex of the reference lead.

If one compares epicardial and endocardial activation in the same heart, it becomes readily evident that endocardial excitation of the left ventricle always precedes excitation of the overlying epicardium by at least 10 msec. On the contrary, in the right ventricle endocardial activity is simultaneous with epicardial activation or may even occur later.

The conclusion follows that in the left ventricular wall the activation front proceeds *from endocardium towards epicardium* along concentric isochrones, while activation of the right ventricular wall must occur mainly in a tangential fashion. A similar pattern, with exclusion of the trabecular region, was found in adult hearts with normal right ventricle.[3] Fig. 5 depicts the activation of the interventricular septum. The heart is the same as the one shown in Figs. 4, 1 and *B*. In this case seven multipolar needle electrodes had been inserted into the septal mass at different levels. The activation which starts in the left central region proceeds smoothly from the left to right in all subendocardial layers and in most of the lower half of the septum.

Approaching the right endocardium, a sudden increase of activation times can be found from point to point, indicating slowing of conduction. *In most of the upper* part of the septum and near the apex on the right side, the activation occurs almost simultaneously at different points on the same level. Therefore the pattern followed by the isochrones indicates that the excitation front advances perpendicularly to the septal endocardium in the central portion

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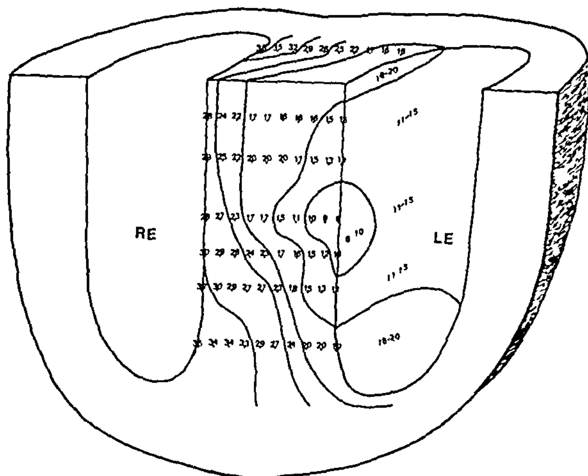


Fig 5 Activation of the interventricular septum *LE* = left endocardium *RE* = right endocardium The anterior apical region is not included in the figure

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Hemodynamic changes during complete heart block in the unanesthetized monkey

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Complete atrioventricular (A V) block produces progressive heart failure and myocardial hypertrophy in dogs and cats[1-3] and cardiomegaly with or without syncopal episodes in man In man heart failure often accompanies complete heart block, but usually the failure is in part related to additional heart disease Children with complete heart block generally have higher idioventricular cardiac rates (40 to 80) than do adults (30 to 60) These observations suggest that both age and species affect the circulatory adjustments made after the onset of complete heart block

In an effort to better understand these mechanisms we studied the changes in regional blood flow that occurred during a six hour period of complete A V block in unanesthetized adult rhesus monkeys with radionuclide labeled microspheres[4] We compared these data with those obtained previously in unanesthetized monkeys during stimulation of the sympathetic nervous system

Methods

Six male monkeys (*Macaca mulatta*) weighing from 4 0 to 8 0 kilograms were used in this study During sodium pentobarbital anesthesia (30 mg per kilogram of body weight) polyvinyl catheters were implanted in the abdominal aorta and vena cava via the iliac vessels and in the left ventricle of the heart via the left common carotid artery The other end of each catheter was brought out through the skin near the umbilicus After recovery, the monkeys were placed in restraining chairs inside sound protected booths each catheter was continuously flushed with lightly heparinized (5 units per milliliter) 0 9 per cent NaCl at 1 ml per hour

Three to five days later complete heart block was produced The animals were anesthetized with sodium pentobarbital and mechanically ventilated with room air Arterial pressures heart rate and an electrocardiogram (ECG) were monitored throughout the procedure After a right

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anterolateral thoracotomy the pericardium was opened and two insulated pacemaker wires (American Cyanamid Company) were sutured in the body of the right ventricle While venous inflow was occluded for 1 5 to 2 5 minutes a right atriotomy was performed and the bundle of His near the A V node was destroyed by either ligature or electrocautery After ECG confirmation of complete A V dissociation the ventricular pacing electrodes were stimulated at the rate that approximated each animal s unanesthetized base line level The chest was closed with drainage the pacing wires were passed subcutaneously to the umbilical area and brought out near the catheters After recovery the monkeys were again placed in a sitting position in their restraining chairs

The experiments were performed five to eight days following the heart block operation An hour before base line measurements were made the booth doors were closed to reduce environmental influences the booths were ventilated and lit as during the previous days Pressure from each catheter was continuously measured with Statham P23 Gb pressure transducers placed at midthoracic levels Before cardiac output was measured a 2 ml arterial blood sample was taken for measurement of hematocrit pH P_{O_2} and P_{CO_2} the latter measured with Radiometer microelectrodes at 38 C Cardiac output was measured in duplicate by the indicator dilution method indocyanine green was injected into the left ventricle and the concentration of dye in blood withdrawn at a constant rate from the aortic catheter was measured using a Waters X302 densitometer Measurements were recorded on a type R Beckman recorder

Directly following the cardiac output measurement distribution of cardiac output was determined with the use of radioactive microspheres This technique allows up to five independent measurements in each animal[4] After base line measurements were obtained the pacemaker was turned off subsequent measurements were made at 15 minutes (second microsphere injection) two hours (third injection) and six hours (fourth injection) Following the fourth injection the pacemaker was restarted (at base line rates) and a fifth set of measurements was made 30 minutes later

For each regional blood flow measurement a batch of 50 μ diameter carbonized microspheres labeled with either [125]I [141]Ce [51]Cr [85]Sr or [95]Nb in 10 ml of 0 9 per cent NaCl was injected over a 15 to 20 second period through the left ventricular catheter Each suspension contained 10 000 to 20 000 microspheres (0 8 to 2 million counts per minute of isotope) which mixed with blood in the left ventricle and was distributed to each organ in direct proportion to organ blood flow Microspheres are trapped in systemic arterioles we have estimated that about 0 1 per cent of the monkey s arterioles are occluded by each batch of microspheres[5]

After the experiment monkeys were killed with an overdose of sodium pentobarbital and all organs and tissues were removed weighed and placed in glass vials each vial was counted for four minutes with a Nuclear Chicago scintillation counter (25 to 30 per cent of skeletal muscle limb bone skin chest wall skull and spine were counted all other organs were counted in their entirety) Counts from the various radionuclides were differentiated as described previously[4] For each determination the fraction of cardiac output to each organ was calculated from the amount of radioactivity in that organ as compared to the total body count for each isotope Flow to each organ was determined by multiplying the percentage of cardiac output to that organ by the dye dilution cardiac output Organ resistance was calculated as the mean driving pressure (mean systemic arterial pressure minus central venous pressure) divided by flow Details of this procedure and estimates of the reliability of measurements and base line values have been previously reported[5,6]

Serial measurements of the same systemic and regional variables and by the same techniques in control monkeys without heart block remained stable during time periods similar to those of the present study[5] The studies with control monkeys also indicated that microsphere infusions do not influence subsequent measurements although total peripheral resistance increases slightly and occasionally transient arrhythmias occur

Table I Hemodynamic measurements before each of the five injections of microspheres for the six experimental monkeys

Measurement	Microsphere injection									
	1 Base line		*2* 15 min after block		*3* 2 hr after block		*4* 6 hr after block		*5* After pacing restarted	
	Mean	*S D*	*Mean*	*S D*	*Mean*	*S D*	*Mean*	*S D*	*Mean*	*S D*
Systolic arterial pressure (mm Hg)	129	17	123	19	119	14	124	13	122	3
Diastolic arterial pressure (mm Hg)	65	12	46*	14	45*	11	49*	12	71	7
Mean arterial pressure (mm Hg)	95	13	75*	17	73*	13	80*	12	93	14
Cardiac output (ml /min /Kg)	264	62	188*	68	145*	86	231	126	304	163
Total peripheral resistance (mm Hg/[L /min /Kg])	368	117	424	119	595*	209	415	174	351	125
Pulse rate (beats/min)	171	13	95*	21	88*	28	92*	33	171	3
Stroke volume (ml /min /Kg)	1 6	0 7	2 0*	0 8	1 8	0 9	2 6*	2 6	1 8	1 1
Left ventricular end diastolic pressure (mm Hg)†	6	11	12*	18	9	12	7	5	5	8
Central venous pressure (mm Hg)†	1	8	8*	10	4	19	2	5	2	8

*Significantly changed from base line ($P < 0\ 05$ paired t test)
†N = 4 measurement values

Results

The over all cardiovascular measurements observed before each of the five microsphere injections are presented in Table I changes in the distribution of cardiac output regional organ blood flows and resistances are shown in Tables II III and IV respectively

Pulse rate and diastolic and mean systemic arterial pressures fell immediately after stopping the pacemaker At 15 minutes these measurements and cardiac output were significantly lower than base line stroke volume left ventricular end diastolic and central venous pressures increased significantly At this time blood was distributed preferentially toward heart brain liver (hepatic artery), skull spine and adrenals at the expense of kidneys skin skeletal muscle spleen, and pancreas Blood vessels in organs that received an increased fraction of cardiac output (except for skull, spine, and adrenals) dilated vessels to those organs receiving a decreased fraction were constricted

Two hours after block systemic arterial pressures and pulse rate were still near those observed at 15 minutes cardiac output had fallen further and total peripheral resistance had increased significantly compared to base line left ventricular end diastolic and central venous pressures fell to nearly base line levels and were unchanged at subsequent measurement periods The pattern of distribution of cardiac output was similar to that found 15 minutes after block except for the kidneys Compared to observations at 15 minutes resistances in each of the measured regional beds showed some increase (except for hepatic artery pancreas and adrenals)

Six hours after block the hemodynamic pattern had changed although diastolic arterial pressure and pulse rate remained lower than base line Cardiac output rose due to increased stroke volume and total

Table II Absolute values in the fraction of cardiac output to selected organs in the six experimental monkeys

	Microsphere injection									
	1 Absolute fraction of cardiac output at base line		*2 15 min after heart block*		*3 2 hr after heart block*		*4 6 hr after heart block*		*5 After pacing restarted*	
	Mean	*S D*	*Mean*	*S D*	*Mean*	*S D*	*Mean*	*S D*	*Mean*	*S D*
Heart	4 2	1	5 8*	1	5 9	1	4 3	1	5 7	2
Brain	6 2	7	9 4	3	10 0	4	9 3*	3	6 6	1
Kidney	17 2	2	13 9	4	15 0	3	14 7	2	13 6	2
Skin	6 2	1	3 7	1	3 9	1	4 7	1	4 6	2
Skeletal muscle	23 8	4	19 0	2	15 8	1	15 7	3	19 4	5
Gastrointestinal organs†	7 0	2	7 1	2	7 4	2	8 5	3	8 3	3
Spleen	2 6	1	1 7	1	1 6	1	1 6	1	2 2	1
Pancreas	1 7	0 4	1 0	0 6	1 2	0 3	1 5	0 3	1 7	0 3
Liver (hepatic artery)	5 9	1	9 2*	2	12 3	3	11 5*	4	8 1	2
Limb bone	3 8	1	4 5	2	4 9	2	6 2	2	5 0	2
Skull and spine	7 9	2	10 0	2	9 4	2	8 9	1	9 6	2
Adrenals	0 2	0 1	0 3	0 1	0 3	0 1	0 3	0 0	0 3	0 0

*S g fica tly ch ged from base l e ($P < 0\ 05$ pai ed t test)
†I cl de stoma h mall and l g int t ne a d cecum

peripheral resistance fell to nearly base line levels Compared to values at two hours all organs except the heart showed some vasodilatation blood flow was preferentially shunted to the brain liver (hepatic artery) limb bone and adrenals at the expense of skin skeletal muscle and spleen However compared to base line measurements absolute values of blood flow were unchanged except for lowered flow to the kidneys skeletal muscle spleen and pancreas

Thirty minutes after the pacing had resumed there were no significant differences compared to base line in any of the systemic hemodynamic measurements regional blood flow or resistances The fraction of cardiac output at this time was increased to the coronary and hepatic arteries skull spine and adrenals that to the kidney skin and skeletal muscle remained decreased

Other organs measured but not included in the tables (eyes lymph nodes lung [bronchial artery] chest wall diaphragm thyroid and fat) had no significant redistribution of cardiac output thus their blood flow and resistance changed in the same proportion as the cardiac output There were no significant changes in Po_2 Pco_2 pH or hematocrit during the experiment

The monkeys showed no gross behavioral effects from the experimental procedure They continued their usual activities and did not struggle or show other signs of discomfort Gross examination of organs at autopsy revealed no consistent pathological changes although in two animals portions of subcutaneous tissue along the catheter tracks showed signs of infection There were no signs of sepsis during life

Discussion

The base line hemodynamic measurements we obtained prior to turning off the pacemaker were not significantly different from those we have obtained in other monkeys[5,6] Thus the heart block operation and period of electrical pacing did not alter the measured cardiovascular variables In comparison to the dog and man the monkey has a high resting heart rate and cardiac index However the percentage

Table III Absolute values for flow (milliliters per 100 Gm) to selected organs in the six experimental monkeys

	Microsphere injection									
	1 Base line		2 15 min after heart block		3 2 hr after heart block		4 6 hr after heart block		5 After pacing restarted	
	Mean	S D	Mean	S D	Mean	S D	Mean	S D	Mean	S D
Heart	317	75	270	82	223*	98	278	77	432	186
Brain	98	37	95	30	77	27	124	57	117	67
Kidney	1138	286	634*	247	614*	211	910*	293	1044	288
Skin	24	8	9*	5	9*	6	18	12	20	17
Skeletal muscle	21	7	12*	6	8*	5	12*	7	20	13
Gastrointestinal organs†	72	24	47*	17	42*	19	72	34	96	52
Spleen	425	49	210*	51	168*	74	268*	57	389	73
Pancreas	320	126	131*	77	137*	81	224*	110	348	103
Liver (hepatic artery)	54	14	55	18	65	40	90	54	84	54
Lungs (bronchial artery)	62	56	45	38	48	27	64	50	79	55
Limb bone	9	3	8	5	8	9	14	12	16	15
Skull and spine	22	9	19	6	15	9	22	12	30	18
Adrenals	227	71	211	132	201	115	276	125	342	184

*Significantly changed from base line ($P < 0.05$ paired t test)
†Includes stomach small and large intestine and cecum

decreases in heart rate and cardiac output that we found after electrical pacing was stopped were similar to those in dogs [2,3,7,9] Our data also show that the monkey like the dog, has an increased pulse pressure total peripheral resistance stroke volume left ventricular end diastolic and central venous pressures during complete heart block We did not observe the six to twelve seconds of asystole that White and associates[8] reported in dogs immediately after cessation of pacing

The increase of cardiac output and stroke volume six hours after the onset of heart block suggests that compensatory influences (such as sodium retention and an increased blood volume), may have begun Compensatory adjustments have been reported much later after A V block [1,2] Central venous and left ventricular end diastolic pressures were near base line values six hours after block, although diastolic and mean systemic arterial pressures were still significantly lower

Except for coronary flow measurements there are few data about the redistribution of cardiac output after onset of complete heart block In unanesthetized dogs[8] the onset of heart block decreased iliac arterial blood flow more than circumflex coronary and mesenteric blood flows and did not change renal flow In unanesthetized monkeys blood flow to skeletal muscle and gastrointestinal organs decreased during heart block but renal blood flow also decreased and did not begin to increase until six hours after heart block

Several reports have noted significant decreases in coronary blood flow in dogs after experimental heart block In anesthetized dogs coronary blood flow was found to be reduced to 50 per cent of preblock values 60 to 90 minutes after section of the bundle of His [7] In the unanesthetized dog White and associates[8] reported that circumflex coronary blood flow decreased 37 per cent a few minutes after cessation of pacing Pitt and Gregg[10] found similar reductions in coronary flow when their dogs were paced at a mean rate of 63 times per minute compared to a mean rate of 152 times per minute In our monkeys coronary blood flow decreased less falling an average of 15 per cent at

Table IV Changes in regional resistances expressed as a per cent of base line values in the six experimental monkeys

	Microsphere injection							
	2 15 min after heart block		3 2 hr after heart block		4 6 hr after heart block		5 After pacing restarted	
	Mean	S.D	Mean	S D	Mean	S D	Mean	S D
Heart	87	34	112	39	109	54	80	30
Brain	80	22	101	31	57	19	107	86
Kidney	150	24	192	58	114	36	130	77
Skin	204	40	?60	48	126	41	147	70
Skeletal muscle	145	24	234*	65	158	45	134	84
Gastrointestinal organs†	121	25	150	63	95	24	88	47
Spleen	186	83	363	133	127	47	127	51
Pancreas	246	59	212	87	115	49	110	68
Liver (hepatic artery)	81	21	81	37	60	37	82	50
Lung (bronchial artery)	187	85	126	109	131	76	117	93
Limb bone	112	50	153	66	66	40	110	107
Skull and spine	95	29	134	57	72	25	90	61
Adrenals	103	53	93	47	64	22	74	35

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15 minutes after block and 30 per cent two hours after block At both these times the coronary vascular bed received an increased fraction of cardiac output coronary flow decreasing less than the cardiac output

Aside from the species difference and the method of creating heart block measurement technique is the most important factor in the interpretation of these discrepant findings Radioactive microspheres do not measure flow continuously but do estimate blood flow without interfering with vessels to major organs Previous studies using unanesthetized dogs[8,10] estimated total coronary flow with previously placed flowmeters on the circumflex branch of the left coronary artery This technique requires extensive surgical manipulation may cause partial occlusion of the artery and assumes that circumflex blood flow represents total coronary flow

Patients with chronic complete heart block and associated myocardial disease have a reduced blood flow to the heart[11] and brain[12] In these studies restoration of normal heart rate by pacing increased blood flow to both brain and heart Our data in monkeys indicate that neither the heart (except at the second hour observation) nor the brain was underperfused during six hours of idioventricular rhythm and that subsequent pacing increased blood flow to the heart but not to the brain These human studies cannot be directly compared to our primate results since older patients with complete heart block generally have extensive coronary atherosclerosis Our observations in adult monkeys may be more comparable to acute heart block in children These patients usually have higher idioventricular rates are often asymptomatic and do not have advanced atherosclerosis

The unanesthetized primate preserves blood flow to the heart brain liver (hepatic artery) bone and adrenals after onset of complete heart block by decreasing blood flow to skeletal muscle gastrointestinal organs and kidneys Six hours after onset of block cardiac output increased toward base line but blood flow to skeletal muscle kidneys spleen and pancreas was still decreased These data suggest that

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Limb bone	112	50	153	66	66	40	110	102
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The unanesthetized primate preserves blood flow to the heart, brain, liver (hepatic artery), bone, and adrenals after onset of complete heart block by decreasing blood flow to skeletal muscle, gastrointestinal organs, and kidneys. Six hours after onset of block, cardiac output increased toward base line but blood flow to skeletal muscle, kidneys, spleen, and pancreas was still decreased. These data suggest that

blood is redistributed after onset of acute heart block until compensatory changes in blood volume are completed and until cardiac output increases toward normal Although we did not measure blood volume or urinary sodium levels, our data indicate that compensatory mechanisms increase cardiac output in monkeys within a few hours after the onset of heart block

The changes in the distribution of cardiac output during acute heart block were similar to those that we have observed in unanesthetized monkeys during hemorrhage [13] In both these experimental conditions the fraction of cardiac output to heart brain, liver (hepatic artery), and adrenals increased at the expense of spleen, pancreas, kidney, skin and muscle With the same preparation we have found a similar pattern of redistribution of blood flow during acute psychological stress[14] and during electrical stimulation of pressor areas of the hypothalamus [15] All these data suggest that at least some of the compensatory adjustments to the bradycardia and hypotension caused by A V block are mediated by an increased discharge from the sympathetic nervous system Gaffney and Braunwald[16] have noted that the adrenergic nervous system plays an important role in the circulatory adjustment of patients with congestive heart failure and that anesthesia may dangerously decrease the sympathetic response that preserves blood flow to vital organs

These experiments indicate that acute heart block in primates without coronary artery disease decreases systemic blood pressure and cardiac output At the same time blood is redistributed to vital organs (heart and brain) at the expense of less important tissues until compensatory mechanisms restore cardiac output toward normal

Summary

After surgically produced complete heart block the hearts of six monkeys were paced electrically for five to eight days at their preoperative heart rates Simultaneous measurements of regional blood flow and other hemodynamic variables were then obtained before and 15 minutes two hours, and six hours after stopping electrical pacing and 30 minutes after restarting pacing Fifteen minutes after stopping pacing heart rate cardiac output and systemic mean and diastolic pressures decreased and stroke volume increased This pattern persisted throughout the six hour period of idioventricular rhythm except that left ventricular end diastolic and central venous pressures were increased only at 15 minutes and cardiac output was not significantly decreased at the six hour period During heart block the fraction of cardiac output received by the heart (except at six hours), brain, liver (hepatic artery), skull spine and adrenals was increased at the expense of skin kidneys (initially), skeletal muscle, spleen and pancreas This pattern of regional redistribution of blood flow is similar to that found during hemorrhage and other conditions in which the sympathetic nervous system is stimulated After pacing was restarted all the systemic variables measured returned to base line levels, and the regional blood flows measured did not differ from those observed before the heart block

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A theoretical approach to the volume pulse wave

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A number of works concerning plethysmography have been done since the early description of the plethysmograph in 1732.[1] The method mainly used has been to obtain information about blood flow through a segment.[11] The segmental blood flow has been evaluated by venous occlusion plethysmography,[2,4,6,7,9,11,13] which was originally described by Brodie and Russell[12] in 1905. Until recently, the value of the venous occlusion plethysmography has been retained as the most reliable method for measuring the rate of total arterial blood flow to the extremity or to a segment of a limb.[13] The limitations of the method, however, are considerable.[14] The greatest theoretical disadvantage of venous occlusion is probably that it may be productive of unaccountable physiological changes in venous, arterial, and lymph flow dynamics.[15] Therefore, the plethysmographer has attempted to analyze a single segmental pulse curve for unrecorded inflow and outflow during a pulse cycle without venous or arterial occlusion. No method up to now has satisfied the experts, due to a lack of precise quantitative information concerning the volume pulse wave.

It is believed that the volume pulse wave is the time course of the difference (Dv) between volume of inflow (Iv) and volume of outflow (Ov).[16] This theory, that may be called "volume difference theory," has been strongly supported. It may be represented by the following equation:

$$D = I - O \qquad (1)$$

Equation (1) means that the amplitude of the volume pulse wave recorded by the plethysmograph for a given moment equals the subtracted value of the volume of outflow from the volume of inflow at the same moment. This is most fundamental to the utilization of the plethysmograph as a tool in clinical medicine. This is, however, too simple for explaining everything about the volume pulse wave. The weakest point of the expression is that one may consider that the volume pulse wave indicates flow volume itself, though it is expressed as the difference between one flow volume and another.

Method

The digital volume pulse was recorded by an Elema Schonander EMT 510 pneumo

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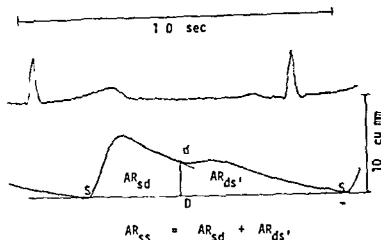


Fig *1* The pattern of volume pulse and the abbreviation of the glossaries S = the starting point of the pulse wave under observation S' = the end of the pulse wave under observation and also the starting point of the successive pulse wave d = the dicrotic notch SD = the time interval from S to d AR_{ss} = the area under the pulse curve over SS' interval AR_{sd} = the area under the pulse curve over SD interval $AR_{ds'}$ = the area under the pulse curve over DS' interval

plethysmograph connected to a Mingograf Cardirex 6T For sensitivity standardization a volume calibration was carried out by pushing the calibration button provided in the EMT 510 to a volume that was adjusted to 10 mm³ The subjects involved in this study were placed in two groups Group A was composed of 40 healthy adults whose ages ranged from 34 to 81 years old and Group B was composed of 24 adults with cardiac disease whose ages ranged from 18 to 80 years old Group B included 11 cases with cardiac failure The subjects rested supine in bed in a comfortable environment The digits studied were usually placed at heart level and sometimes above or below heart level for special observations In order to observe the effect of venous occlusion on the pulse wave form the brachial vein was occluded by inflation of the cuff wrapped about the arm for several seconds The plethysmographic cup was placed on the tip of the finger defined as that portion of the finger distal near the terminal interphalangeal articulation The pattern of volume pulse and abbreviation of glossaries are shown in Figs 1 and 2 Areas under the pulse curve over SD SS' and DS' are named AR_{sd} AR_{ss} and $AR_{ds'}$ respectively (Fig 1) The areas were measured graphically A tangent line was drawn along the steepest part of the ascending limb of the pulse curve (Fig 2) The intersections of this line with the base line and the apex line are named a and b The time interval between a and b is expressed by Δt which is the so-called inclination time The height of b point from the base line is expressed by Δv which is equal to the maximum amplitude of the pulse wave The area under the pulse curve over SB is shown by AR_b One may draw a line which is parallel to the base line and

$$\frac{AR_b}{SB}$$

apart from the base line The intersection of this line with the steepest part of the pulse curve is denoted as p The amplitude of the pulse wave at p is expressed by Δv_p

Results

As shown in Fig 1 the whole area of the pulse wave ($AR_{ss'}$) can be divided into two parts—i e AR_{sd} and $AR_{ds'}$ When one looks at these areas one may notice that the size of AR_{sd} correlates to that of $AR_{ds'}$ regardless of whether the size of the pulse wave is great or small Therefore a normal ratio of AR_{sd} to $AR_{ds'}$ could be obtained from Group A and an abnormal ratio if present from Group B It should be noticed however that the ratio

$$\frac{AR_{sd}}{AR_{ds'}}$$

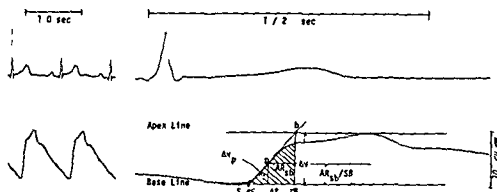


Fig 2 The abbreviation of glossaries dv/dt = A tangent is drawn to the steepest part of the ascending limb of the pulse wave The time interval between the intersection of this line with the base line *(a)* and the apex line *(b)* makes up the inclination time (Δt)[11] The maximum amplitude of the volume pulse is equal to Δ AR_{sb} is the area under the pulse curve over the SB interval A parallel line to the base line which is AR_{sb}/SB apart from the base line can be drawn The intersection of this line with the steepest part of the pulse curve is denoted as p The rate of rise of the pulse wave at the point p is given by

$$\lim_{\Delta t \to 0} \Delta v/\Delta t = dv/dt$$

SB = the time interval from S to b AR_{sb} = the area under the pulse curve over the time interval between S and b

being within normal limits might be based on the normal ratio

$$\frac{SD}{DS}$$

and that the abnormal ratio

$$\frac{AR_{sd}}{AR_d}$$

might be based on the abnormal ratio

$$\frac{SD}{DS'}$$

though the ratio

$$\frac{AR_d}{AR_d}$$

may have more information than that of the ratio

$$\frac{SD}{DS}$$

In order to find the clinical meaning which the ratios

$$\frac{AR_d}{AR_d}$$

and

$$\frac{AR_d}{AR}$$

might have the values of

$$\frac{AR_{sd}}{SD}, \frac{AR_d}{DS}$$

and

$$\frac{AR}{SS}$$

were calculated They also closely correlate with each other as shown in Figs 3 and 4 The mean values of the ratio

$$\frac{\frac{AR_{sd}}{SD}}{\frac{AR_d}{DS}}$$

instead of

$$\frac{AR_{sd}}{AP_d}$$

and of the ratio

$$\frac{\frac{AR_d}{SD}}{\frac{AR}{SS}}$$

instead of

$$\frac{AR_d}{AR}$$

were obtained from Group A and B (Table I) The differences between the mean values obtained from Group A and that from Group B were statistically significant

The correlation between

$$dv/dt$$

and

$$\frac{AR_b}{SB}$$

defined in Fig 2 can be seen in Fig 5

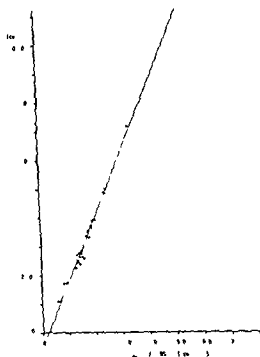


Fig 3 Correlation between AR_{sd}/SD (Y axis) and AR_{sd}/DS' (X axis) in 93 pulse waves obtained from normal subjects $r = 0.94$ $P < 0.00005$ regression line $Y = 2.2\ X - 0.53$

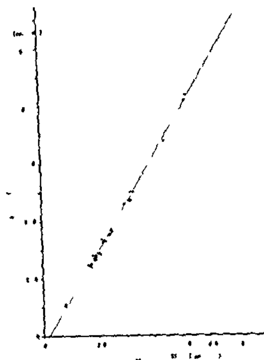


Fig 4 Correlation between AR_{sd}/SD (Y axis) and $AR\ /SS$ (X axis) in 93 pulse waves obtained from normal subjects. $r = 0.98$ $P < 0.00005$ regression line $Y = 1.6\ X - 0.38$

Changes of the amplitude of the volume pulse wave and the ratio

$$\frac{d\ /dt}{\frac{AR_{s}}{SB}}$$

by venous occlusion are shown in Figs 6 and 7 and their mean values are listed in Table II The difference between the mean value of control and that of venous occlusion was statistically significant in Group A ($P < 0.00005$) but it was not in Group B ($P < 0.1$)

Discussion

At the beginning of the discussion let us try to interpret the actual changes of the pulse wave due to venous occlusion and postural alteration of the limb according to the volume difference theory

The venous occlusion plethysmographic method of measuring the segmental blood flow is based on the assumption that the initial rate of swelling of the part which indicates the rate of arterial inflow during venous occlusion is the same as the actual undisturbed rate of arterial inflow immediately before the venous occlusion If the assumption is accepted it can be thought that the arterial inflow to the digit (I) must be kept unchanged immediately after venous occlusion Venous drainage (O) is obviously decreased by the occlusion Therefore volume difference (D) should be increased by the occlusion while the amplitude of the pulse wave actually becomes decreased (Fig 6)

When the digit studied is raised above the heart the amplitude of the volume pulse is actually increased [17,18] According to the volume difference theory the size of volume pulsation depends directly on the quantity of the volume difference (D) If the quantity of the volume difference is large enough in comparison with the volume of blood flow the blood must be progressively accumulating in some part of the vessels If the quantity of the volume difference is very small in comparison with the volume of blood flow, the volume difference

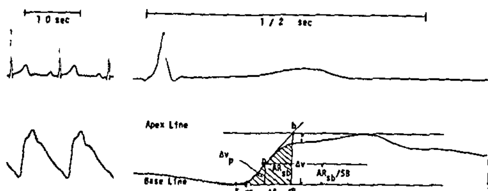


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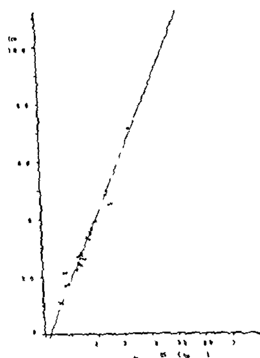


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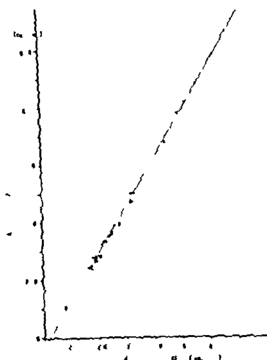


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Changes of the amplitude of the volume pulse wave and the ratio

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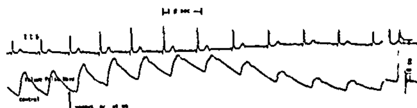


Fig 6 Demon tration of waveforms obtained with venous occlu ion The venous occlu ion cuff was applied to the arm just above the elbow crease and was inflated to a pres ure less than diastolic

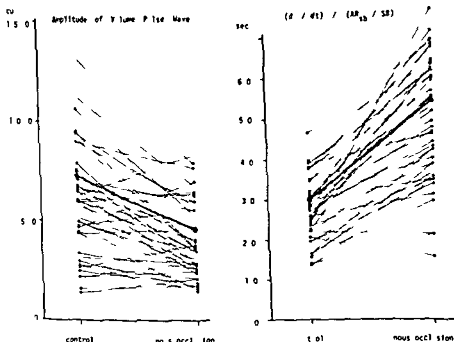


Fig 7 Changes in the ratio $(dv/dt)/(AR_{sb}/SB)$ and in the amplitude of the pul e wave observed in Group \ due to enous occlusion Mean values of the ratio were elevated from 29 9 sec $^{-1}$ to 53 8 sec $^{-1}$ while those of the amplitude decreased from 7 3 mm^3 to 4 6 mm^3

sidered as a constant during the single pulse cycle started at S Equation (7) seems to represent clearly the displacement de flection of the volume pulse but it has ap proximation involved in the application of Equations (4) and (5) to the digit that has non Hookean blood vessel with inertia and non ideal fluid flow

According to the representation of the volume values reported by Burch[22] five thousand mm^3 of finger tip the pulse wave of which was 7 mm^3 contained 800 mm^3 of blood If the volume pulsation comes from venules and capillaries[11] the average velocities of the blood flow and pulse wave are about 2 cm per second and 200 cm per second respectively[23] The size of the pulse wave calculated by Equation (7) is 8 mm^3 ($\kappa = 1$) while reported ize was 7 mm^3 The calculated value is not very different from the actual value

Let us try to interpret the meanings of the areas and ratios according to an appli cation of Equation (7) to them The areas can be defined as

$$AR_{sd} = \int_{S}^{D} \Delta v \; d = \frac{1}{c} \int_{S}^{D} \overline{U} \; dr \qquad (8)$$

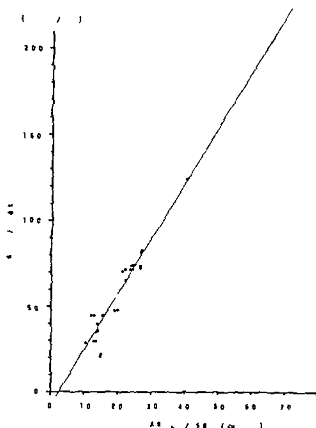


Fig 5 Correlation between (dv/dt) (Y axis) and AR_{sb}/SB (X axis) in 93 pulse waves obtained from normal subjects $r = 0.69$ $P < 0.00005$ regression line $Y = 33X - 9$

might be involved in the pulsatile change of the blood flow That is, the higher amplitude of the volume pulse should be due to the increased volume flow However there is no report that the blood flow of the digit is increased by raising the arm On the contrary there are many reports that the blood flow was reduced when the digit was raised [17,18] Lack of correlation between blood flow and pulsation volume is often observed [13] It should be noticed that the pulsation volume does not indicate blood flow itself One more disadvantage of Equation (1) is that it is very difficult to interpret the meanings of the areas and ratios

$$AR_d \quad AR \quad AR_d \quad \frac{AR_d SS}{AR \quad SD} \quad \frac{AR_{sd} DS'}{AR_d \quad SD}$$

and

$$\frac{dv/dt}{\frac{AR_b}{SB}}$$

Of course it is convenient to have a theory which can explain everything concerning volume pulse One theoretical proposal for this purpose will be presented in the following section

Let us consider a single straight cylindrical blood vessel instead of a network of small vessels in the digit studied The resting radius of the cylindrical vessel, its longitudinal length, and its radial dilatation are denoted by *R*, *L* and *ξ*, *respectively*

The resting volume of the vessel (V) is given by

$$V = \pi R^2 L \qquad (2)$$

The volume increment of the vessel following radial dilatation due to pulsatile flow is given by

$$\Delta\bar{v} = \pi (2 \xi R + \xi^2) L \qquad (3)$$

According to Womersley[20] the radial dilatation is related to the velocity of flow, thus

$$\frac{2\xi}{R} = \frac{\bar{U}}{c} \qquad (4)^*$$

where $\bar{U}$ is the average velocity of the blood flow and c is the wave velocity From Equations (3) and (4) if $\bar{U}/4c << 1$ then the volume change of the vessel is given by

$$\Delta v = \frac{\pi R^2 L \bar{U}}{c} \qquad (5)$$

It is obvious that the volume change of the digit (Δv) depends on the volume change of the blood vessel ($\Delta\bar{v}$) in it The volume change of the digit—i e the displacement deflection of the volume pulse wave is given by

$$\Delta v = \kappa \Delta\bar{v} \qquad (6)$$

where κ is a constant which relates to the elasticity of the tissue surrounding the vessel

From Equations (2) (5) and (6) the displacement deflection of the volume pulse at a given moment (τ) during a single pulse cycle started at S can be written by

$$\Delta v = \frac{\kappa V \bar{U}_\tau}{c} \qquad (7)$$

The resting volume of the vessel is con

*Derivation of the equation is based on the ideal fluid thin walled Hookean tube neglecting the inertia of the wall It is also assumed that the radius of the tube in equilibrium under internal pressure is equal to its radius under zero transwall pressure [20,21,24,25]

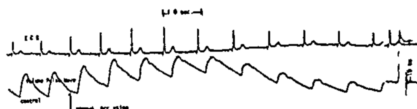


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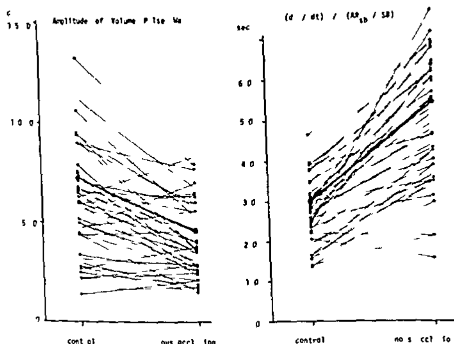


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Let us try to interpret the meanings of the areas and ratios according to an application of Equation (7) to them The areas can be defined as

$$AR_{sd} = \int_{s}^{D} \Delta v \; dt = \frac{\kappa \, l}{c} \int_{s}^{D} \overline{U} \; d \qquad (8)$$

Table I Mean values of the ratios obtained from two groups

	Group A	Group B	
	Normal control	Cases with cardiac disease	Cases with cardiac failure
$\frac{AR_{sd}\ DS}{AR_d\ \ SD}$	2 05 ± 0 43*†	1 83 ± 0 28*	1 61 ± 0 21†
$\frac{AR_{sd}\ SS}{AR\ \ SD}$	1 49 ± 0 15‡§	1 45 ± 0 16§	1 29 ± 0 10‡

*Difference statistically significant to P < 0 05
†Difference statistically significant to P < 0 005
‡Difference statistically significant to P < 0 0001
§Difference not statistically significant

Table II Mean values of (dv/dt) / (AR_{sb}/SB) obtained from two groups

	Group A	Group B	
	Normal control	Cases with cardiac disease	Cases with cardiac failure
Control	29 9 ± 5 1*†‡	31 9 ± 9 5*§	34 5 ± 9 1†‖
Venous occlusion	53 8 ± 19 7‡	37 9 ± 11 0§	37 6 ± 13 0‖

*Difference not statistically significant
†Difference not statistically significant
‡Difference statistically significant to P < 0 00005 (high significance)
§Difference not statistically significant
‖Difference not statistically significant

and

$$AR_d = \int_D^S \Delta v \ d\tau = \frac{\kappa V}{c} \int_D^S \overline{U} \ d\tau \qquad (10)$$

If we define the mean values of average velocity during the period of SD SS' and DS', ($\overline{\overline{U}}_{sd}$ $\overline{\overline{U}}_{ss}$ and $\overline{\overline{U}}_d$) as

$$\overline{\overline{U}}_{sd} = \frac{1}{SD} \int_S^D \overline{U} \ d\tau$$

$$\overline{\overline{U}} = \frac{1}{SS'} \int_S^S \overline{U} \ d\tau$$

and

$$\overline{\overline{U}}_d = \frac{1}{DS} \int_D^S \overline{U} \ d\tau$$

Equations (8) (9) and (10) can be reduced to

$$AR_{sd} = \frac{\kappa V \overline{\overline{U}}_{sd} SD}{c} \qquad (11)$$

$$AR = \frac{\kappa V \overline{\overline{U}} \ \ SS}{c} \qquad (12)$$

and

$$AR_d = \frac{\kappa V \overline{\overline{U}}_d \ \ DS}{c} \qquad (13)$$

respectively

From Equations (11), (12) and (11) (13) the ratios are given by

$$\frac{AR_{sd}}{AR} = \frac{\overline{\overline{L}}_{sd}}{\overline{\overline{L}}} \qquad (14)$$

and

$$\frac{AR_{sd}}{AR_d} = \frac{\bar{L}_{sd}}{\bar{L}_d} \quad (15)$$

where $\bar{L}_{sd}$ $\bar{L}$ and $\bar{L}_d$ are the mean dis placements of the blood during SD SS, and DS respectively It is obvious that they closely correlate with one another One may also easily obtain the ratios of velocities of blood flow corresponding to

$$\frac{SD}{SS}$$

and

$$\frac{SD}{DS}$$

as follows

$$\frac{AR_{sd}\ SS}{AR\quad SD} = \frac{\bar{\bar{U}}_{sd}}{\bar{U}} \quad (16)$$

and

$$\frac{AR_{sd}\, DS'}{AR_d\quad SD} = \frac{\bar{\bar{U}}_{sd}}{\bar{U}_d} \quad (17)$$

The difference between the mean values of the ratios of the normal persons and those with cardiac disease or cardiac failure can be explained as the difference between the mean values of average velocities during SD and those during DS' corresponding to each group

Next application of Equation (7) is to AR_b which is the area under the volume pulse over SB interval That is

$$AR_b = \int_S^B \Delta v \;\, d\tau = \frac{\kappa V}{c} \int_S^B \bar{U} \;\, d\tau \quad (18)$$

If the mean value of the average velocity of flow during SB ($\bar{U}_b$) is defined as

$$\bar{\bar{U}}_{sb} = \frac{1}{SB} \int_S^B \bar{U} \;\, d\tau$$

Equation (18) can be reduced to

$$AR_b = \frac{V\, \bar{\bar{U}}_{sb}\, SB}{c} \quad (19)$$

The amplitude of the volume pulse at a point p that was shown in Fig 2 can be expressed a

$$\Delta v_p = \frac{\kappa\, V\, \bar{U}_p}{c} \quad (20)$$

The maximum rate of rise in the pulse wave at the point p is given by

$$\lim_{\Delta t \to 0} \frac{\Delta v}{\Delta t} = \frac{dv}{dt} = \frac{\kappa V}{c} \frac{d\bar{U}_p}{dt} \quad (21)$$

Thus the acceleration of the blood flow is due to the influences of some unbalanced force (F) on the blood mass (m) in the cylindrical vessel the force acting on the blood mass at the moment p can be described as

$$F = \frac{d(m\, \bar{\bar{U}}_p)}{dt} = \frac{mc}{V} \frac{dv}{dt} \quad (22)$$

If force (F) is expressed by pressure (P)

$$P = \frac{cm}{VA} \frac{dv}{dt} \quad (23)$$

where A is the total area on which the force is acting

From Equations (19) and (23) the ratio of

$$\frac{dv}{dt}$$

to

$$\frac{AR_b}{SB}$$

is given by

$$\frac{dv/dt}{AR_b/SB} = \frac{A}{m} \frac{P}{\bar{\bar{U}}_{sb}} \quad (24)$$

According to the Poiseuille law governing laminar flow in a cylindrical tube pressure drop (P) is expressed as

$$P = \frac{8\,\mu\, L\, \bar{U}}{R^2} \quad (25)$$

where μ is the viscosity L the length of the vessel $\bar{U}$ the mean velocity of flow and R the radius of the vessel If *Poiseuille's* formula is applicable to a steady flow com ponent—the mean flow—of the pulsatile arterial flow Equation (24) can be rewrit ten as

$$\frac{dv/dt}{AR_b/SB} = \frac{K\quad A}{m} \quad (26)$$

where K is the peripheral resistance

The reason for the constancy of the ratio

$$\frac{dv/dt}{AR_b/SB}$$

is due to the constancy of the peripheral resistance (Fig 5) Highly significant differences between the mean values of ratio observed in normal control and those changed by venous occlusion can be explained by the increase of the peripheral resistance that is probably due to a drop in the mean velocity of the blood flow (Fig 7) In Group B, values of the ratio were not significantly changed by venous occlusion because of the underlying high peripheral resistance in the cases of persons with cardiac disease or cardiac failure (Table II)

The effect of venous occlusion on the amplitude of the volume pulse can be explained by a decrease of flow velocity and an increase of wave velocity It is clear that the decrease in the flow velocity is caused by a decreased pressure gradient between the mean pressure of the arteriole and that of the venule and the increased peripheral resistance as shown in the elevation of the ratio

$$\frac{dv/dt}{AR_b/SB}$$

(Fig 7) The wave velocity is expressed by Bramwell and Hill[26] as follows

$$c = k\sqrt{V \quad dp/dv}$$

where k is a constant and V is the initial arterial volume per unit length The increase in the wave velocity can be clearly explained by the increased bulk modulus

$$V \quad \frac{dp}{dv}$$

in the equation due to venous congestion

When the digit is raised above the heart the amplitude of the pulse wave should become larger because of the decreased velocity of the pulse wave and a slightly increased velocity in the flow It is clear that the velocity of the pulse wave becomes slower because of a reduction in the bulk modulus As reported by Holling and Verel,[17] the fall in systolic and diastolic arterial pressure that accompanies an elevation of the arm corresponds to the change in hydrostatic pressure The pulse pressure does not significantly alter as the arm is lifted When the arm is lifted, the venous pressure falls slightly but not below 1 to −3 mm Hg, though the brachial venous pressure is 2 to 5 mm Hg at heart level These findings indicate that the pressure gradient between the mean pressure of the arteriole and that of the venule remains constant or slightly increases with an elevation of the arm The ratio

$$\frac{(dv/dt)}{(AR_b/SB)}$$

indicating peripheral resistance does not alter by an elevation of the arm (Fig 5) Therefore it might be considered that the average velocity of the flow is almost equal to the control or is slightly increased when the arm is lifted

The deviation of the base line of the pulse wave seen in the venous occlusion method can be explained by the increment of the resting volume (V) in Equation (7) The principle of the method might be based on the possibility that the increment of the resting volume caused by arterial inflow under no venous return must be proportional to the degree of deviation of the base line If the ratio of flow velocity to wave velocity is not significantly altered by the venous occlusion it is possible to measure blood flow by the method

Summary

One simple equation is proposed for a representation of the volume pulse wave

$$\Delta v = \frac{\kappa V \bar{U}}{c}$$

where Δv is the volume change of the digit studied—i e the amplitude of the pulse wave at a given moment T κ constant V the resting volume of the blood vessel $\bar{U}_T$ the average velocity of the blood flow at the given moment and c the wave velocity

$$\frac{AR_s}{SD} \quad \frac{AR_d}{DS}$$

and

$$\frac{AR}{SS}$$

are closely correlated with each other The constancy of the ratios

$$\frac{AR_s}{SD} \Big/ \frac{AR_d}{DS} \quad \frac{AR_s}{SD} \Big/ \frac{AR}{SS}$$

can be explained as follows

$$\frac{AR_{sd}\ SS}{AR\ \ SD} = \frac{\bar{\bar{U}}_{sd}}{\bar{\bar{U}}}$$

$$\frac{AR_{sd}\ DS}{AR_{d}\ \ SD} = \frac{\bar{\bar{U}}_{sd}}{\bar{\bar{U}}_{d}}$$

where $\bar{\bar{U}}_{d}$ $\bar{\bar{U}}_{4}$ and $\bar{\bar{U}}$ are the mean values of the average velocity of the flow during SD DS and SS' respectively

The ratio of the rate of rise of the pulse wave

$$dv/dt$$

to

$$\frac{AR_{b}}{SB}$$

is also constant under normal conditions AR_{b} signifies the area under the pulse wave during SB The ratio can be expressed as

$$\frac{dv/dt}{AR_{b}/SB} = \frac{K\ \ A}{m}$$

where K is the peripheral resistance A the total area on which the force is acting and m the blood mass on which the force is acting

To obtain the values K $\bar{\bar{U}}$ c and K having clinical significance through the analysis of the volume pulse further advance of the method should be expected

We are very grateful to Dr Ichiro Matsubara for his valuable advice

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Case reports

Infection of an avulsed papillary muscle tip simulating bacterial endocarditis

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Rupture of a papillary muscle usually initiates a series of events that terminates within hours or days in cardiac decompensation and death[1,2] However a few patients have developed only moderate mitral insufficiency and lived for months with a ruptured papillary muscle[4] This report describes a patient who had a ruptured papillary muscle for an indeterminate length of time this condition being called to medical attention by the presence of gram negative bacteremia which persisted despite appropriate antimicrobial therapy Clinically this was thought to represent bacterial endocarditis with ruptured chordae tendineae At postmortem examination the patient s illness was found to be caused by persistent infection of an avulsed papillary muscle tip

Case report

The patient was a 74 year old man with diabetes Six weeks prior to admission he noted the onset of anorexia nausea postprandial fullness and weight loss Three weeks later he began having diaphoresis chills and fever to 106 F A white blood cell count of 10 000 per mm^3 and a hemoglobin of 13 Gm per 100 ml were observed at his local hospital Five days of intravenous tetracycline failed to alter his course and he was admitted to the Vanderbilt University Hospital

Mild dyspnea on exertion had been present for several months but the patient denied orthopnea paroxysmal nocturnal dyspnea or chest discomfort There was no history of rheumatic fever or myocardial infarction A soft systolic murmur at the apex was present a year prior to admission

The diagnosis of diabetes mellitus had been made 10 years previously and he had taken insulin for six years. He was receiving no other medicine at the time of admission A left below the knee amputation had been done 15 months earlier because of vascular insufficiency Urinary frequency and hesitancy had been present for several years

Physical findings included a supine blood pressure of 104/54 mm Hg a regular pulse of 92 per minute and a rectal temperature of 101 F Splinter hemorrhages conjunctival petechiae and splenomegaly were noted Examination of the chest revealed no abnormalities There was no jugular venous distention at 45 degrees The heart was not enlarged

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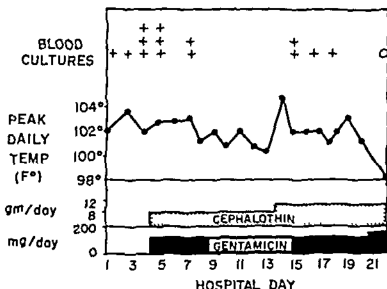


Fig 1 Schematic representation of clinical course

The first heart sound and a systolic click were palpable The click occurred early in systole and was followed by a harsh III/VI murmur that lasted throughout the rest of systole The murmur was heard along the left sternal border and at the cardiac apex with radiation to the axilla There were no bruits over the stump of the left lower extremity Right costovertebral angle tenderness was present The prostate was firm and enlarged

Initial laboratory studies revealed a white blood cell count of 10 100 per mm³ with 89 per cent segmented forms Some of the neutrophils contained toxic granulations The hematocrit was 36 per cent platelet count 333 000 per mm³ and the latex fixation test for rheumatoid factor was negative The blood urea nitrogen was 23 mg per 100 ml and glucose 370 mg per 100 ml Examination of the urine showed 4+ sugar without acetone There was microscopic hematuria

Two blood cultures drawn during the first 24 hours after admission were positive for *Klebsiella pneumoniae* (Fig 1) and the admission urine culture also yielded *Klebsiella pneumoniae* in a concentration greater than 100 000 organisms per ml with identical sensitivities to the organism in the blood

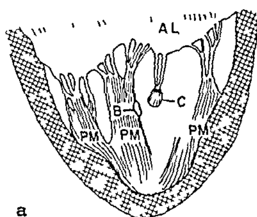
The clinical impressions were that the patient had *Klebsiella* endocarditis with ruptured chordae tendineae resulting in mitral insufficiency Therapy was instituted with intramuscular gentamicin 5 mg per kilogram of body weight per day and intravenous cephalothin 8 Gm per day Some of the laboratory and clinical features of his hospital course are presented in Fig 1 The minimal bactericidal concentrations of cephalothin and gentamicin for the *Klebsiella* isolated from the patient s blood were 6 2 µg per milliliter and 0 39 µg per milliliter respectively His serum was bactericidal for the *Klebsiella* when diluted 1 8 on the fourth day of therapy and 1 16 on the sixth day of therapy This indicated that serum levels of antimicrobial activity usually considered adequate in treating endocarditis were being achieved Nevertheless the patient remained febrile and blood cultures were repeatedly positive for *Klebsiella* Subsequent urine cultures were negative

Daily examination of the patient abdominal films two intravenous pyelograms a barium enema gall bladder series thoracolumbar spine films and a liver scan failed to reveal a source of bacteremia other than the heart A progressive deterioration in renal function ensued with the serum urea nitrogen and creatinine reaching 72 mg per 100 ml and 7 8 mg per 100 ml respectively Because of the severity of the underlying medical problems mitral valve replacement was deferred and antibiotic therapy was continued

The admission ECG showed normal sinus rhythm with low voltage in the limb leads and non specific ST T wave changes On the twentieth hospital day he was noted for the first time to have an irregular pulse An ECG at this time revealed supraventricular premature contractions and short bursts of supraventricular tachycardia with aberrant ventricular conduction Digitalis was administered cautiously On the next day he became hypotensive and died

At necropsy the heart weighed 300 Gm The right and left atria were moderately dilated but the other chambers were not enlarged The aortic pulmonary and tricuspid valves were not remarkable The mitral valve ring measured 8 5 cm and the valve appeared normal with no gross evidence of recent or remote endocarditis All mitral leaflet chordae tendineae were attached and were not thickened or inflamed The aortic leaflet of the mitral valve was remarkable in that the most central chordae were not fixed to the ventricular surface due to an avulsion of part of the papillary muscle (Fig 2)

The avulsed piece of papillary muscle measured 10 by 7 by 6 mm was yellowish white and was attached to the valve by normal appearing chordae tendineae The previous point of attachment of this portion of papillary muscle was not readily apparent on gross examination Both anterolateral and posteromedial papillary muscles had smooth surfaces and showed minimal focal subendocardial fibrosis However microscopic examination of the anterolateral papillary muscle revealed remote myocardial







b

Fig 2 *a* through *c* *a* Schematic illustration and photograph of gross specimen of patient's heart Posterior section through the left ventricle illustrating the ruptured papillary muscle tip (*C*) attached to the aortic leaflet of the mitral valve (*AL*) by its chordae tendineae *B* indicates the base of the papillary muscle at the site of rupture Papillary muscles are labeled *PM* *b* Photomicrograph showing the base of the papillary muscle at the site of rupture There are no bacteria and there is no evidence of inflammatory reaction (Hematoxylin and eosin Original magnification ×435) *c* Photomicrograph demonstrating gram negative bacilli in the center of the avulsed tip and the absence of inflammatory infiltrate (Gram's stain Original magnification ×2,?70)

necrosis calcification and mild chronic inflammation presumably at the site of avulsion of the papillary muscle fragment (Fig 2) Search of multiple sections of the anterolateral papillary muscle base showed no abscesses and no bacteria were seen on gram stained sections (Fig 2*b*) In contrast the avulsed papillary tip was teeming with gram negative bacilli (Fig 2) No inflammatory cells were seen among the bacteria nor was any viable muscle found The tissue of the avulsed tip was eosinophilic and had the appearance of autolyzed cardiac muscle Despite the lack of support due to the avulsed papillary muscle tip the aortic leaflet of the mitral valve was anchored by other chordae tendineae from both the anterior and posterior papillary muscles

The coronary arteries showed calcification and marked atherosclerosis Although narrowed no point of obstruction or thrombosis was found Multiple sections of the left ventricular myocardium failed to reveal recent or remote infarction

Each kidney weighed 200 Gm with multiple small scars over the surface Microscopic section of the kidneys showed arterial and arteriolar nephrosclerosis There was chronic inflammation present in the cortex and medulla of both kidneys The prostate was enlarged and showed glandular hyperplasia and microabscesses

Comments

The patient was admitted to the hospital with a history very suggestive of bacterial endocarditis The physical findings of a heart murmur fever petechiae enlarged spleen anemia and splinter hemorrhages were especially convincing *This impression* was strengthened by multiple positive blood cultures and a urine culture positive for *Klebsiella* The infection however was persistent in spite of appropriate treatment and only at necropsy was its location found to be the avulsed papillary muscle tip In

attempting to correlate the necropsy findings with his clinical course several aspects *of the illness deserve comment* The etiology of the disease of the mitral apparatus is especially perplexing

The etiologies, pathology and pathophysiology of mitral regurgitation have been a topic of much interest in recent years *Rheumatic mitral regurgitation* with pathological involvement of the mitral leaflets has become proportionately much *less frequent* as the spectrum of mitral regurgitation has become better defined Any portion of the mitral valve apparatus or its attachments may become diseased in a manner to create regurgitation Physical findings and the clinical course may be characteristic for a given etiology

Papillary muscle dysfunction is an extremely common etiology for mitral regurgitation ischemic heart disease being the entity usually responsible for this variety of mitral regurgitation The murmur of *papillary muscle dysfunction is non holo*systolic and usually relatively localized to the apical area Ordinarily few symptoms *are present and endocarditis is not a com*plication Papillary muscle rupture occurs most often in association with acute myo*cardial infarction and is characteristically* associated with a pan systolic murmur of great intensity It is customary for pro*found left ventricular failure to occur* at the time of rupture Elongation of the chordae tendineae can account for mitral regurgitation which is usually associated with characteristic physical findings including a systolic click and a crescendo decrescendo systolic murmur These patients ordinarily do not have symptoms Trauma is a very rare cause for isolated chordae rupture

Our patient does not fit characteristically into any of the categories of mitral regurgitation described above The documentation of a systolic murmur prior to the onset of the illness suggests that the papillary muscle ruptured before the infective process developed This is in contrast to an instance of myocardial abscess reported by Hackel and Kaufman[5] In their patient, a new mitral murmur appeared and the patient rapidly deteriorated Autopsy demonstrated that the papillary muscle was detached from the ventricle Microscopic sections of *both* the ventricle and papillary muscle revealed abscess formation at the edges of the separation with gram negative bacteria being present

The separated papillary muscle tip of our patient was found to have undergone complete necrosis and was without inflammatory reaction Many gram negative bacilli were present in this avulsed papillary tip In contrast and unlike the patient reported by Hackel and Kaufman,[5] neither necrosis, inflammatory reaction, nor bacteria were present in the base of the papillary muscle at the site of separation of the tip Hence it seems unlikely that an abscess with subsequent rupture of the papillary muscle is the explanation in this case It is probable that the papillary muscle rupture antedated the infection This would explain why his illness presented principally as an infectious disease and not importantly as myocardial dysfunction

Two findings may explain the mild hemodynamic effects of the ruptured papillary muscle (1) the aortic leaflet was anchored by chordae tendineae from the remainder *of the anterolateral as well as the pos*teromedial papillary muscles and more importantly (2) the fragment that ruptured *from the main body of the papillary muscle* was small so that only 2 of the 18 chordae that anchored the mitral valve apparatus were lost The resulting dysfunction of the mitral valve was apparently minimal and was indicated only by the systolic click and the murmur of mitral insufficiency rather than by congestive heart failure

A postulated sequence of events proceeds as follows the small papillary muscle tip ruptured but caused only minimal hemodynamic disturbance The patient's chronic *Klebsiella* urinary tract infection produced a transient *Klebsiella* bacteremia which infected the free floating tip Because of its avascular nature the tip acted as an infected foreign body analogous to a prosthetic heart valve In such avascular tissues adequate tissue levels of antibiotics are *frequently not obtained and phagocytes are* unable to gain access to the lesion Thus sustained bacteremia continued despite the presence of what are usually considered to be adequate serum bactericidal levels of antibiotics to which the organism was sensitive Eradication of infections in such avas

cular structures is extremely difficult and usually requires antibiotic therapy plus surgical removal of the intravascular foreign body[6]

To our knowledge this is the first report of a ruptured papillary muscle presenting clinically as bacterial endocarditis and sustained bacteremia Our experience has been similar to that of McHenry and associates[7] in that sustained bacteremia despite appropriate antimicrobial therapy has usually been associated with undrained abscesses infection of foreign bodies such as prosthetic heart valves contaminated intravenous fluids and lines or severe burns When a sustained bacteremia despite appropriate antimicrobial therapy occurs in association with mitral insufficiency serious consideration should be given to the possibility of an infection of an avascular portion of the mitral apparatus

We thank Dr Howard E Rosen for permitting us to report this patient.

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Left-to-right shunt at atrial level after rupture of papillary muscle from acute myocardial infarction

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A systolic murmur may develop during or after acute myocardial infarction from ischemia, necrosis fibrosis, or rupture of a papillary muscle or from rupture of the ventricular septum Differentiation of mitral regurgitation from ventricular septal rupture in this setting may be difficult but the distinction is often made by the detection of a high oxygen content of blood in the pulmonary artery strongly suggesting the presence of a ventricular septal defect Rarely, mitral regurgitation produces retrograde flow through the pulmonary capillary bed causing elevation of the pulmonary arterial oxygen content [1] We recently studied a patient who, during acute myocardial infarction developed increased blood oxygen content in the right side of the heart due to papillary muscle rupture and a newly acquired left to right shunt at atrial level Hemodynamic data indicated that the shunt was located at the atrial level, and necropsy showed that the defect was due to stretching of the fossa ovale region by left atrial dilatation after the acute development of mitral regurgitation Pertinent clinical and anatomic features of this patient are summarized in this report

Case report

W A (021 39 50) a 65 year old man who died August 13 1970 was first seen at Georgetown University Hospital on August 4 1970 An acute diaphragmatic wall myocardial infarction had occurred 75 days earlier when he had been admitted to another hospital Six days after the onset of infarction he developed a loud holosystolic apical murmur and severe congestive cardiac failure Despite bed rest digitalis diuretics and salt restriction during the next 69 days he remained in chronic heart failure and became cachectic The electrocardiograms (ECG s) taken by his private physician in previous years specifically showed none of the ECG features of atrial septal defect and his previous chest roentgenograms were normal

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Fig 1 Left ventricular cineangiogram in the left anterior oblique view There is a herniation of the atrial septum (*arrows*) with contrast material cros ing from the left to the right atrium Rad opaque dye can be seen in the left ventricle aorta and left atrium The visible catheter is in the right atrium and right ventricle but the tip in the pulmonary artery is not visible The left ventricular catheter cannot be seen



Fig 2 Surg cal spec men of the mitral valve leaflets and supporting structures That portion of the posteromedial papillary muscle which had ruptured i smooth and endothelialized (*arrow*)

Right heart catheterization at Georgetown University Hospital showed pulmonary hypertension and disproportionate elevation of the pulmonary arterial wedge V waves indicating m tral regurgitation (Table 1) The hydrogen inhalation test with the platinum t pped electrode in the right atrium yielded an appearance time of 3 seconds document ng a left to-r ght shunt at atrial level Krypton 85 inhalation test with simultaneous blood sampling from pulmonary and left brachial arteries (on two occasions) yielded a calculated pulmonary to-systemic flow ratio in excess of 4 1 Left ventricular cineangiography disclosed moderately severe m tral regurgitation A well-defined portion of the atrial septum bulged into the right atrium and contrast material pas ed from the left atrium to the right atrium at that position (Fig 1)

At operation on August 13 1970 portions of the posteromedial papillary muscle were found detached from its main trunk (Fig 2) The ruptured

Left-to-right shunt at atrial level after rupture of papillary muscle from acute myocardial infarction

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A systolic murmur may develop during or after acute myocardial infarction from ischemia, necrosis, fibrosis, or rupture of a papillary muscle or from rupture of the ventricular septum. Differentiation of mitral regurgitation from ventricular septal rupture in this setting may be difficult but the distinction is often made by the detection of a high oxygen content of blood in the pulmonary artery, strongly suggesting the presence of a ventricular septal defect. Rarely, mitral regurgitation produces retrograde flow through the pulmonary capillary bed causing elevation of the pulmonary arterial oxygen content.[1] We recently studied a patient who, during acute myocardial infarction, developed increased blood oxygen content in the right side of the heart due to papillary muscle rupture and a newly acquired left-to-right shunt at atrial level. Hemodynamic data indicated that the shunt was located at the atrial level, and necropsy showed that the defect was due to stretching of the fossa ovalis region by left atrial dilatation after the acute development of mitral regurgitation. Pertinent clinical and anatomic features of this patient are summarized in this report.

Case report

W. A. (021-19-50), a 64-year-old man who died August 11, 1970, was first seen at Georgetown University Hospital on August 1, 1970. An acute diaphragmatic wall myocardial infarction had occurred 23 days earlier, when he had been admitted to another hospital. Six days after the onset of infarction he developed a loud holosystolic apical murmur and severe congestive cardiac failure. Despite bed rest, digitalis, diuretics, and salt restriction during the next 10 days, he remained in chronic heart failure and became cachectic. The electrocardiograms (ECG) taken by his private physician in previous years specifically showed none of the ECG features of atrial septal defect and his previous chest roentgenograms were normal.

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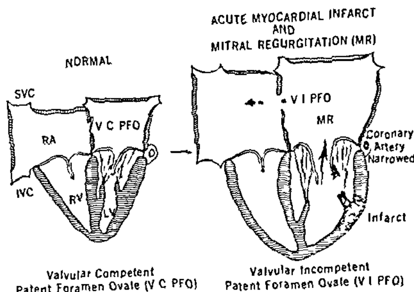


Fig 4 Diagrammatic representation of a valvular-competent patent foramen ovale in contrast to a valvular incompetent patent foramen ovale following *myocardial infarction* and mitral regurgitation The left atrial walls have been stretched so that the valve of the patent foramen ovale can no longer cover the defect

Table I Cardiac catheterisation data

Site	*Pressure (mm Hg)*	*Site*	*Pressure (mm Hg)*
Right atrium	a = 9 v = 21 mean = 9	Pulmonary artery wedge	a = 25 v = 37 mean = 26
Right ventricle	54/8	Left ventricle	115/29
Pulmonary artery	62/21 mean = 40	Brachial artery	117/92 mean = 108

ventricular septal perforation on the basis of a step up in oxygen saturation in the right ventricle unless *a left to* right shunt at atrial level has been excluded

Summary

Clinical and necropsy observations are described in a patient who developed a large left to right shunt at atrial level after rupture of a papillary muscle during *acute* myocardial infarction Attention is called to the importance of differentiating this combination from rupture of the ventricular septum and from mitral regurgitation resulting from papillary muscle necrosis with or without rupture

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Fig. 3. *A* and *B*. *A*, View of the atrial septum from the right atrium. The fossa ovale is herniating through the atrial septum. *B*, View of the atrial septum from the left atrium. The fossa ovale is bulging into the right atrium creating the atrial septal defect. Black silk sutures have closed the surgical atriotomy which is in the interatrial groove.

portion contained about half the chordae tendineae attached to the posteromedial muscle. The atrial septum in the area of the fossa ovale was stretched and redundant, thereby bulging into the right atrium producing a 1.0 cm sized defect which represented a valvular incompetent patent foramen ovale. This defect was closed by suture. The mitral valve was excised and was replaced by a size 19 Hufnagel disc prosthesis. The patient could not be weaned from extracorporeal circulation.

At necropsy (70A-376) the left atrium was large and the fossa ovale was aneurysmally dilated. A portion of the fossa ovale herniated into the right atrium enlarging a foramen ovale which had probably been valvular-competent although probe-patent before the rupture of the papillary muscle (Fig. 3).

Discussion

Papillary muscle rupture as a complication of acute myocardial infarction is rare.[2] Two large necropsy series discovered only two out of 6,000 and three out of 14,000 cases respectively.[3] In 1948 Davison[4] made the first antemortem diagnosis, and in 1957 Sanders and colleagues[5] compiled 56 cases from the literature and added five new ones. Cederquist and Soderstrom[6] reported a four year necropsy study in 1964, including 569 patients dying of acute myocardial infarction, from a total of 4,741 cases examined. They found a 0.9 per cent incidence of papillary muscle rupture. Mitral valve replacement has been successful in a number of these patients.[7]

The frequency of ventricular septal perforation complicating acute myocardial infarction is probably about 1 per cent.[8,9] Rupture of the ventricular septum classically occurs between 4 and 11 days after acute myocardial infarction and thus overlaps the period during which papillary muscle rupture occurs. The left to right shunt may cause biventricular heart failure.[10,11]

Mitral valve disease may be associated with left to right shunt at atrial level but usually it is due to rheumatic mitral stenosis and/or insufficiency, rupture of chordae tendineae, or congenital mitral atresia.[2,14] Following acute myocardial infarction and papillary muscle rupture, our patient developed such a shunt from dilatation of the left atrium so that the foramen ovale which previously had been valvular competent although patent was stretched and became valvular incompetent (Fig. 4). Cases of papillary muscle rupture previously reported have not demonstrated interatrial shunting even though shunts were specifically sought.[15,16] In rupture of chordae tendineae, however, either spontaneously or after infective endocarditis, interatrial shunting has occurred.[17,18] Since about 20 to 25 per cent of adults studied at necropsy have valvular-competent but patent foramen ovales[19] as did this patient, it is possible that an interatrial communication might follow acute severe mitral regurgitation of any etiology.

Thus the finding of oxygenated blood in the main pulmonary arteries in patients with acute myocardial infarction and newly acquired systolic precordial murmurs may be due to left to right shunting at atrial level from stretching of the membrane covering the fossa ovale, or from reflux through the capillary bed, or through a shunt at ventricular level. Care should be taken not to diagnose the presence of a

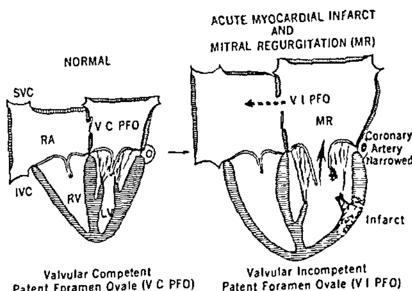


Fig 4 Diagrammatic representation of a valvular competent patent foramen ovale in contrast to a valvular incompetent patent foramen ovale following myocardial infarction and mitral regurgitation The left atrial wall have been tretched so that the valve of the patent foramen ovale can no longer cover the defect

Table I Cardiac catheterisation data

Site	*Pressure (mm Hg)*	*Site*	*Pressure (mm Hg)*
Right atrium	a = 9 v = 21 mean = 9	Pulmonary artery wedge	a = 25 v = 57 mean = 26
Right ventricle	54/8	Left ventricle	115/29
Pulmonary artery	62/21 mean = 40	Brachial artery	117/9? mean = 108

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New approach in treatment of cardiac decompensation in U S S R

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The routine treatment of cardiac decompensation with cardiac glycosides and diuretics has not changed essentially during the past decades It is common experience that the therapeutic effect decreases with the severity of decompensation and the *frequent side effects* of digitalization are disturbing In some individual patients the threshold between beneficial and side effects of digitalis therapy is narrow In the United States and Great Britain considerable work *has been done* to improve diuretic therapy to lessen side effects and toxic effects and to produce diuresis in intractable failure

In Russia recent studies in management of heart failure have been aimed at *bio*chemical reactions in the heart muscle itself Maslyuk and associates[1] and Klykov[2] working simultaneously but probably independently have attempted to develop a new approach for the treatment of heart failure based on Meerson s *pioneering* work[3,4] on experimental ventricular hypertrophy and decompensation including hemodynamic macroscopic and microscopic structural changes biochemical changes and energetics changes of the ECG and changes in the autonomic and central nervous system (cardiovascular and conditioned reflexes EEG) Meerson s earlier results publi hed in two monographs[3,4] and numerous articles were reviewed ten years ago[5] Already at that time the material (500 rabbits 50 dogs with experimental aortic stenosis) was impressive and has been considerably enlarged since then Biochemical changes were and are the central focus of Meerson s investigations

During the development of experimental left ventricular hypertrophy synthesis of protein and amino acids is increased and declines in the terminal decompensation The increase of ATPase during development of hypertrophy indicating improved capacity of myosin for dephosphorylation of ATP was considered by Meerson as one *of the* principal compensatory factors enabling the myocardium to cope with the increased load Its decrease in the later phases of hypertrophy was found to signal approaching cardiac decompensation Meerson assumed that donors of free *SH* groups (cysteine methionine) may counteract the decrease of ATPase in heart failure and thus exert a beneficial effect and this was experimentally confirmed administration of a combination of methionine vitamin B12 and ATP in experimental aortic stenosis in rabbits counteracted the terminal decrease of ATPase and DNA Meerson s work was paralleled by Western investigators[6,8] however refer

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ences to Western literature are kept to a minimum in the limited scope of this review Meerson[9] has considerably expanded the scope of his work, including various types of ventricular hypertrophy (in arterial hyper tension, valvular disease coronary insuf ficiency, congenital heart disease and toxic cardiac damage) and found the underlying mechanism quite similar This was true also for the response to environmental stresses (hypoxia, cold) Meerson[9] recently sum marized his work and proposed a general hypothesis of the genesis of cardiac hyper trophy and terminal decompensation

Of the numerous results, two are par ticularly pertinent as a basis for the de velopment of the new therapeutic ap proaches (1) inhibition of the increase of synthesis of proteins and nucleic acids pre vents the development of compensatory hypertrophy in experimental left ventricu lar hypertrophy, and (2) administration of inhibitors of protein and nucleic acid synthesis in animals with developed ven tricular hypertrophy produces rapid cardiac decompensation [10]

In both studies,[1,2] the treatment with preparations stimulating protein synthesis supplemented the conventional treatment with cardiac glycosides Meerson and col leagues[11] and Klykov[12] have shown that the cardiotonic effect of cardiac glycosides was increased by a combination with preparations, activating the synthesis of nucleic acids particularly vitamin B12, folic acid, pantothenic calcium, and SH donors, were found to be effective in pre venting or ameliorating strophantin intoxi cation (Klykov,[12] Maslyuk and Fedorova[13])

The purpose and design of both studies was similar but there were some differences in sample size, functions tested evaluation and preparations used

Preparations used and rationale

Maslyuk and associates[1] investigated the effect of various preparations in three treat ment groups supplementing cardiac gly cosides and diuretics

Treatment Group A Potassium orotate, 0 5 Gm , 3 times daily 1 to 1½ hours be fore meals Orotic acid is a precursor in pyrimidin synthesis and is thought to stimu late the synthesis of proteins

Treatment Group B ATP, 1 ml (10 mg), 2 times daily intramuscular vitamin B12, subcutaneous injection 200 mcg daily, methionine orally 0 25 Gm , 3 times daily While only a negligible part of injected ATP enters the cell, the breakdown prod ucts of ATP (AMP and ADP) stimulate oxidative phosphorylation in mitochondria Vitamin B12 stimulates synthesis of thy mine, thymidin, and desoxyribose which are precursors for DNA synthesis Methi onine as donor of SH groups may prevent decrease of ATPase activity of myosin

Treatment Group C Calcium panto thenate 250 mg , 3 times a day, orally or 1 ml of 20 per cent solution 2 times intra muscular Pantothenic acid contains ace tylcoenzyme A involved in carbohydrate and fat metabolism It is decreased in cardiac decompensation [14]

Control Group Full therapeutic doses of digitalis preparations (orally) and intra venous strophantin in periods of acute right or left ventricular failure

Klykov[2] used a combination of vitamin B12, 500 mcg daily, folic acid 0 02 Gm , 3 times daily as stimulant and source for formation of high energy phosphates, ATP sodium, 1 ml (10 mg) 2 times daily intra muscular, calcium pantothenate 0 1 to 0 2 Gm 3 times daily, and *Unitiol* (sodium 2 3-dimercaptopropane sulfonate) as donor of SH groups 5 ml of 5 per cent solution 1 to 2 times daily intramuscular KCl 3 Gm per day All patients control and treatment groups received intravenous strophantin 0 5 ml of 0 05 per cent solu tion, and diuretics (hypothiazid) Patients with rheumatic heart disease received also aspirin

Samples

In both studies patients with cardiac decompensation of categories IIA, IIB III were used This classification * generally used in the U S S R is like other classifi

*Classification of cardiac decompensation (G B Lang)

Phase I Compensated at rest Symptoms of decompensation only in physical work dyspnea e cessive tachy card a decrease of work capacity (fatigue)

II Decompensation at rest (edema pulmonary conges- tion)

A Disturbance of hemodynamics comparatively mild usually responds well to treatment

B Pro ounced stagnation of circulation in organs, however without sig ificant disturbance of their functions Therapy less effective

III Terminal or dystrophic decompensation. Severe disturbance of hemodynamics. Stable changes of metaboli m and functions irreversibl histological changes Work capacity completely abed

*Table I Effect of treatment (in per cent) of patients in each category of cardiac decompensation for four groups**

Effect of treatment (per cent)	Control group			Treatment group A			Treatment group B			Treatment g oup C		
	Phase			Phase			Phase			Phase		
	IIA	IIB	III	IIA	IIB	III	IIA	IIB	III	IIA	IIB	III
Excellent	47†	16	4	97	68	19	91	66	32	87	67	56
Sati factory	45	51	30	0	32	56	0	25	41	13	33	33
Fair	4	24	32	0	0	25	7	7	21	0	0	11
Absent	1	9	34	3	0	0	2	2	6	0	0	0

*G roup re (1) co tr l (ca d c glycosid s and d r tics) (2) tre tment group A (orot te calcium in add tion to glycosid s and d u retic) (3) treatm t g o p B (ATP v tam B12 a d m thionine i ad lition to glycosid and d uretics) (4) treatment group C (calcium p tothenat dd t n to glycos.des a d d uretics)
†Dat re tabulated f m informat contained in Fig 1 Maslyuk and colleag es.[1]

cations somewhat arbitrary and probably involves considerable observer variation However in the hand of the same ob servers it provides probably a fairly reli able separation as to the degree of de compensation There is no doubt that these stages reflect progressive phases of de compensation Maslyuk and colleagues sample[1] of 500 patients was subdivided into four groups the control group of 251 patients receiving digitalis and diuretics and three treatment groups—A B and C (together 249 patients)—receiving different preparations as listed above in addition to digitalis and diuretics The number of patients in the three categories (IIA IIB III) are not listed but control and treat ment groups were compared for the same category of decompensation

Klykov s sample (48 controls 48 treat ment) was considerably smaller but con trol and treatment groups were well matched as to age sex and phase of de compensation The average age of the con trol group was 53 years and that of the treatment group was 52 5 years There is no information how well the 4 groups in Maslyuk and associates sample[1] were matched but it may be assumed that they were fairly randomized because of the large sample size The diet in the control and treatment groups was standardized Both samples included vario is etiologies coro nary insufficiency congenital and acquired valvular disease and rheumatic carditis

A breakdown into these different types of underlying cardiac disease was given in Klykov s[3] study but was incomplete in Maslyuk and colleagues report[1] It ap pears that both studies were reasonably well controlled but a double blind design would have been superior At least the control groups should have been given placebos in addition to the conventional digitalis therapy and both patients and hospital personnel should have been un aware who received the placebos and who received the treatment It is obvious that this might affect the subjective symptoms rather than objective findings but sub jective symptoms are essential for the clinical judgment of therapeutic effects

Methods

The clinical judgment of therapeutic effects was based on subjective symptoms decrease of cyanosis and hydration (hydro thorax pulmonary congestion ascites liver size peripheral edema) decrease of respira tory and heart rate diuresis etc in addi tion to investigation of various hemo dynamic functions ECG and blood chem istry

Results

Clinical course Table I shows the effect of treatment of the four groups in Maslyuk and colleagues study[1] subdivided as to the phase of decompensation (IIA IIB and III) in terms of excellent satisfactory

fair and absent. Table I shows a highly favorable effect of the supplemental treatment in groups A, B and C in all phases of decompensation (IIA, IIB, III) as compared to the conventional treatment with cardiac glycosides and diuretics. The increase of excellent results in the most severe category of decompensation (III) particularly in Group C is impressive, as well as the absence of a missing therapeutic effect: all patients showed improvement during one month of treatment with pantothenate calcium. Consequently, under the effect of treatment many patients originally in category III shifted to category IIB or IIA and from IIB to IIA. The need for diuretics decreased significantly for category IIA and IIB in all treatment groups (A to C).

The results in Klykov's study were similar. In the control group the effect of conventional treatment (digitalis, diuretics) was excellent in 14 (29 per cent), satisfactory in 24 (50 per cent), absent in 9 (21 per cent). In the treatment group an excellent effect was noted in 36 (75 per cent); eight of 11 patients originally in category III were reclassified into categories IIB or IIA. Since subjective symptoms were involved in the general judgment of therapeutic effect, the results are somewhat questionable in the absence of placebo controls. More specific information about the changes of subjective and objective clinical symptoms of cardiac decompensation would have been preferable. However, it appears to be likely that the considerable improvement is not alone psychogenic. In view of this situation, objective criteria are more pertinent for the evaluation of therapeutic effects.

Objective criteria. In Maslyuk and associates' study[1] the supplemental treatment reduced the incidence of digitalis intoxication (Table II) in all treatment groups A, B, C—particularly in group B (ATP, vitamin B12, methionine) and category III—and was assumed to be due to the effect of free SH groups. ST depression and T inversion improved to a greater extent in all treatment groups than in the control group, which may also be due in part to a reduction of digitalis effect.

Table III shows a condensation of Klykov's results of biochemical and hemodynamic changes. There is a greater increase of free SH groups in blood and serum potassium, and a greater decrease of blood pyruvate in the treatment group than in the control group. The changes in the treatment group are highly significant while the changes in the control group did not reach the level of statistical significance.

In both groups there was a highly significant decrease of venous pressure, of general and pulmonary circulation time and of the heart rate, but more so in the treatment group. The statistical significance of the difference in the changes in control versus treatment group was not calculated. Respiratory rate decreased significantly in the treatment group, but not in the control group. There was a significant improvement of the mechanics of systole in the treatment group, in contrast in the control group the changes were slight or absent. Particularly impressive is the dramatically faster speed of the increase of intraventricular pressure in the treatment group. Addition of normal values for the items listed in Table III would have been informative.*

For analysis of changes in the mechanical systole, Maslyuk and associates[1] divided the sample into several sub groups: for decompensation IIA (1) patients with mitral disease, (2) patients with aortic and mitral valvular disease; for patients in decompensation category IIB and III, subgroup (3) patients with mitral disease and subgroup (4) aortic mitral valvular disease. In the control group, statistically significant improvement of the parameters of mechanical systole (shortening of isometric phase, lengthening of ejection phase and faster increase of ventricular pressure) were found in subgroups (1) and (2) after treatment with cardiac glycosides. The changes in decompensation categories IIB and III were not statistically significant.

The favorable changes were more pronounced in the treatment groups. In the treatment group A (orotate potassium) significant improvement of systolic parameters were found in subgroups (1) to (3)—

*For normal values of ventricular ejection time and isovolumic contraction time (corresponding approximately to isometric phase) we refer to Aronow[13] and Weissler[14].

Table II *Effect of treatment on incidence of digitalis intoxication**

Phas	Control g oup			Treatment group A			Treatment group B			Treatment group C		
	IIA	IIB	III	II1	IIB	III	II1	IIB	III	IIA	IIB	III
Incidence (%) of pronounced bradycardia	23	37	45	7	9	31	15	8	12	10	14	27
Frequent PVCs (bi eminy)	13	17	50	0	6	13	2	4	12	10	14	25

Dat re t bulated fr m information co ta ed in Fig 4 M dyuk a d associat s[1]

Table III *Changes of hemodynamic functions and blood chemistry in treatment g oup and control group**

Blood chemistry and hemodynamics	Treatment group (N = 43)					Control group (N = 45)				
	Before treatment		After treatment			Before treatment		After treatment		
	M†	SD	M	SD	P	M	SD	M	SD	P
SH groups (m /equ %)	56 9	1 8	66 8	1 6	<0 001	5 8	2 0	6 5	7 1	>0 05
Pyruvic acid (mg%)	1 66	0 11	0 94	0 04	<0 001	1 96	0 19	1 91	0 18	>0 05
Potassium (mg %)	1? 5	0 6	17 8	0 9	<0 001	16 5	1 1	15 1	1 1	>0 1
Hemodynamics										
Venous pressure (mm. [H2O])	19	11 9	133	3	<0 001	150	9 9	125	10 0	<0 01
Circulation times (sec)	39 1	1	4 6	0 9	<0 001	32 8	1 8	?7 4	1 7	<0 001
Pulmonary circulation time (sec)	1 9	0 7	8 ?	0 3	<0 001	11 9	0 5	10 7	0 4	<0 001
Heart rate	88 9	9	7? ?	1 5	<0 001	89 2	? 3	80 9	1 6	<0 01
Respiration rate	?7 7	0 7	?0 7	0 5	<0 001	?6	0 8	?5 0	0 9	>0 20
Isometric contraction phase (msec)	51	3 0	??	? 0	<0 001	49	3	49	?	>0 5
Ejection period (msec)	1?	5 0	49	5 0	<0 001	?09	6	214	6	>0 ?
Initial speed of increase of intraventricular press. (mm./Hg/sec)	1 493	81	4 167	337	<0 001	1 6?9	14?	1 574	73	<0 05

*Tre tm t g up = f l acid, ATP l ol v am B12 i dd tio to t opha t and d uret cs contr l gr p = str ph t d a d d retics. D t re co d sed f om Tabl 1 to III Klyk 1

†Abbre ati ns M = mean al s SD = ta d d d iati

i e including decompensation categories IIB and III In treatment group B (ATP etc) significant improvement was found in all subgroups (1) to (4) The difference of the changes between control and treatment group B was statistically significant for all subgroups (1) to (4) The changes of electrokymographic indices also favored the treatment groups

Table IV shows a summary of the results of s. che parameters in per cent of incidence of improvement no changes and deterioration The effect of the supplementary treatment is most obvious in the more advanced categories of decompensation IIB and III—i e in conditions with about 45 per cent of failure of the conventional therapy with cardiac glyco ides

In patients with decompensation category IIA hemodynamic indices improved in controls as well as in treatment groups without significant differences between con

fair and absent. Table I shows a highly favorable effect of the supplemental treatment in groups A, B, and C in all phases of decompensation (IIA, IIB, III) as compared to the conventional treatment with cardiac glycosides and diuretics. The increase of excellent results in the most severe category of decompensation (III), particularly in Group C, is impressive, as well as the absence of a missing therapeutic effect; all patients showed improvement during one month of treatment with pantothenate calcium. Consequently, under the effect of treatment many patients originally in category III shifted to category IIB or IIA, and from IIB to IIA. The need for diuretics decreased significantly for category IIA and IIB in all treatment groups (A to C).

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Table IV Changes of parameters of systole during treatment

Changes in per cent of patients	Decompensation categories					
	IIA			IIB and III		
	Control (cardiac glycosides)	A Orotate + cardiac glycosides	B ATP B12 etc + cardiac glycosides	Control (cardiac glycosides)	A Orotate + cardiac glycosides	B ATP B12 etc + cardiac glycosides
Improvement	70 10	74 3	75 0	54 6	72 7	74 2
No change	21 65	25 7	25 0	11 8	22 8	20 0
Deterioration	8 25	0	0	33 6	4 5	5 8

trols and treatment groups In more severe decompensation (IIB and III), the cardiac minute volume increased 0 4 L per minute in the control group, 1 0 L per minute in the treatment group A (difference to controls significant at p <0 05 level), and 1 03 L per minute (p < 0 05) in treatment group B

Venous pressure decreased in the control group by 39 5 mm H_2O in treatment group A by 61 8 mm (difference to controls p = 0 01) and in treatment group B by 80 3 mm (p < 0 05) circulation time decreased in controls 3 4 seconds in treatment group B 8 mm (difference to controls of 4 6 p < 0 01) and in treatment group C 6 6 mm (p < 0 02)

Thus, in hemodynamic indices as well as in the systolic parameters the favorable effect of the supplementary treatment is more evident in severe cardiac decompensation (IIB, III) than in mild decompensation (IIA)

The significantly greater improvement of various objective indices in the treatment groups as compared to the controls substantiates the general judgment of improved clinical course (Table I) and the improvement of subjective symptoms not specifically listed but included in Table I is in all likelihood secondary to the objective improvement of circulation rather than psychogenic

Conclusions

It appears that the merit of supplementary treatment of cardiac decompensation with preparations related to protein synthesis is sufficiently documented to hold promise for further exploration

Summary

Based on Meerson s fundamental work[3] on the genesis of ventricular hypertrophy and decompensation Russian investigators supplemented the conventional therapy of cardiac decompensation with preparations related to the synthesis of protein and nucleic acids The merit of the supplemental treatment was shown in the clinical course as well as in various objective criteria (blood chemistry hemodynamics systolic parameters ECG) The reported results are highly significant and the method merits trial in other centers

We wish to thank Dr R M Gabrielson of Warner Chilcott Laboratories Morris Plains N J for information about the composition of Unitiol and Dr N V Klykov for supplemental information

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Different authors have defined sudden death in coronary heart disease in different ways. In order to make international comparisons concerning sudden non traumatic death possible an international expert group agreed in 1970 on the following definition. Sudden unexpected natural death is defined as death occurring immediately or within an estimated period of time of 24 hours after the onset of acute objective or subjective symptoms[10]. Some authors have used 1 hour instead of 24 hours as the criterion[11 12]

Sudden death in acute coronary heart disease

It must be emphasized that not all cases of sudden death especially when the 24 hour interval is used are caused by heart disease. Subarachnoidal bleeding, other major sudden hemorrhages, massive infections and pulmonary embolism can also lead to death within such a short interval of time. Most persons who die suddenly however do so because of heart conditions. Kuller[4] reported a study in which 32 per cent of all deaths selected by random sampling were sudden. Sixty per cent of these were considered to be due to acute coronary heart disease[4]. Spain and coworkers[14] performed a similar investigation in New York and found that a high percentage of sudden deaths was due to heart diseases.

The prerequisite for a scientific analysis of cases of sudden death is a high incidence of autopsy. In Gothenburg Sweden the incidence of autopsy is over 90 per cent both in individuals who die in hospital and those who die outside hospital. Forty five per cent of all patients over 65 years of age who suffered acute myocardial infarction during one year died before arriving in hospital. Under the age of 65 years the corresponding figure was 25 per cent[15]

Approximately half of all sudden deaths are thus due to coronary heart disease. It must however be emphasized that a large part of the patients who die suddenly do not reveal signs of myocardial infarction during autopsy but do exhibit advanced coronary disease. The latter patients often reveal scars due to previous infarcts[4 5 16]. It has been pointed out that it may not be possible to equate patients who die suddenly without pathological anatomical signs of myocardial infarction with those who die similar deaths and who have developed myocardial necrosis[17]. In the extensive World Health Organization study in coronary heart disease and sudden death it was found that there was a high incidence of patients who lacked thrombosis in the coronary arteries but had pathologic anatomically demonstrable myocardial necrosis. they nevertheless died within one hour of the onset of symptoms[18]. Refined methods of investigation including histochemical staining of autopsy preparations may produce other results[19]

From the study in Tecumseh Michigan 98 deaths due to coronary disease occurred during the six year follow up period 45 of which occurred within one hour of the onset of symptoms[12]

In the Framingham study[11] 156 persons died before reaching the age of 65 years during the 14 year follow up period 120 men and 36 women. One hundred twenty of these 156 deaths were due to coronary disease.

In that study sudden death was defined as death occurring within one hour of the reappearance of acute symptoms. Two thirds of the 120 deaths in coronary disease occurred outside the hospital. Sixty two of these were sudden deaths as defined above. Younger persons and men were somewhat over represented among those who died suddenly while older persons or women had symptoms for a longer time. Of the 120 deaths in coronary disease 53 concerned persons in whom this disease had not previously been diagnosed while 67 of the patients had had diagnosed coronary heart disease before dying. Of these 49 had suffered myocardial infarction. Fifty-one of the 120 had been investigated not more than two years previously and had been classified as completely free from heart disease. It is probable that investigation nearer the time of death—e g at an interval of 6 months would have revealed heart changes. It is concluded that a very high proportion of the deaths which occur suddenly involve individuals who have not previously had serious signs of heart disease.

In a study of labile angina in Edinburgh

Fundamentals of clinical cardiology

Sudden death: Identification of high risk groups

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A substantial number of sudden coronary deaths occur under circumstances which preclude effective treatment. The present paper surveys background knowledge and tries to identify persons with a high risk of future sudden death in order to make the evaluation of primary and secondary preventive efforts effective.

History

In Western Europe and The United States of America cardiovascular diseases are the predominating causes of death.[1,2] Approximately 50 per cent of men aged between 50 and 64 years who die die of various cardiovascular diseases. In women up to the age of 65 years the share of the total mortality rate occupied by cardiovascular diseases is less than in men, but it rises successively with increasing age until it reaches the same level.[2] Coronary heart disease is the cause of approximately two thirds of the cardiovascular deaths in men and the cause of about one third of cardiovascular deaths in women aged 55 years. With increasing age, the proportion remains relatively stationary in men but increases in women, reaching 55 per cent at the age of 75 years.[2]

In acute episodes of myocardial infarction most patients die outside the hospital. In various studies it has been reported that between 50 and 70 per cent of all deaths in acute myocardial infarction occur before the patient reaches hospital care.[3-6]

Only in a very small proportion of the deaths has the deceased taken immediate steps to attempt to establish contact with medical assistance. In a study recently performed in Stockholm this was true for less than 10 per cent of the patients.[7] The cause of this low figure is partly the short interval between the sudden onset of symptoms and death.

It is also partly due to the patients who, after the acute onset of symptoms, do not appreciate the gravity of the situation or do not wish to trouble a doctor at inconvenient times (e.g., middle of the night). This so called 'patient delay' is difficult to measure and has varied in different studies.[8,9]

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infarction within one hour of the appearance of symptoms but was not correlated with the 3 week mortality rate

In the Tecumseh population the incidence of systolic or diastolic hypertension high relative weight and hyperglycemia was found to be higher in those dying suddenly than for the population as a whole *Multiple risk factors were especially common* in those dying suddenly [12]

Premonitory symptoms

Prodromal symptoms were demonstrated in 50 to 70 per cent of the patients with myocardial infarction on their arrival in the hospital [50, 53] Among the patients who died suddenly prodromal symptoms are difficult to study Kinlen[54] found symptoms from the upper abdomen and chest in 33 per cent *of those who died suddenly and these symptoms* either appeared or became altered during the month immediately prior to death Kuller and associates[4, 5] found that 24 per cent of those who died suddenly in coronary disease had visited the physician during the week before dying The cause of these visits however could not be ascertained Kinlen[54] and also Lindstrom[55] (Table I) found that half of those who died had visited a doctor during the 2 to 4 weeks *immediately before dying* [54, 55] As has previously been pointed out coronary heart disease commences with sudden death in about one fifth of the cases Analysis of these deaths however shows that very few individuals were normal before dying In Kuller's[4, 5] study from Baltimore 92 had diabetes hypertension cerebral hemorrhage or had visited a physician during the month prior to dying or had been admitted to hospital during the year before dying In the Tecumseh study only one of the 45 who died suddenly had been free from previous illness risk factors and ECG *abnormalities* in the first cross sectional investigation [12]

Arrhythmias in the population

The lethal mechanism in acute heart death has been considered to be malignant ventricular arrhythmias The extent of arrhythmias in the population or parts of it has been difficult to assess In studies of life insurance companies in the U S A the mortality risk was reported to be greater

Table I Time between last contact with a doctor and death in Gothenburg (consecutive cases during three months)

	No autopsy	Fresh M I	Other heart changes
0-2 days (n = 7)	4	2	1
3 14 days (n = 11)	1	4	6
The last year (n = 12)	1	4	7
No known contact (n = 5)	2	1	2

M I = myocardial infarction

when premature contractions were present on the ECG The increase in risk was small but significant [56, 57] Prospective population studies confirm the increased risk of death [11, 12, 58, 59] In the Tecumseh study 98 individuals died in coronary disease during the six year follow up period Forty five of these deaths occurred within one hour of the appearance of symptoms In all but seven of these disturbances of rhythm or conduction had previously been observed on the resting ECG Ten of these patients (22 per cent) had premature ventricular contractions at rest long before the terminal episode In all premature contractions were noted in 165 individuals over 30 years of age and among the 3 459 individuals who were free from arrhythmias 35 died suddenly In the individuals with premature ventricular contractions this is equivalent to a sudden death mortality rate of 61 per 1 000 compared to 10 per 1 000 amongst the individuals who were free from premature contractions Of the ten deaths among individuals with premature contractions 7 occurred in persons over 60 years of age The occurrence of premature ventricular contractions was correlated to the occurrence of the coronary disease The influence of other cardiovascular risk factors was not checked statistically in this study However no definite connection between accepted cardiovascular risk factors and the tendency to premature ventricular contractions was found The authors therefore speculated whether the premature ven

Fulton and others[20] have also studied the question of sudden death Of 380 patients with symptoms suggesting myocardial ischemia, 167 had what was called "unstable angina, or labile angina Three of these died suddenly and 23 developed acute myocardial infarction within three months During the same period there were 79 cases of sudden death within the same area the majority of whom had not, as far as is known, previously experienced pain in the chest Approximately half of them had consulted a physician for various complaints but these could not be related to myocardial ischemia during the previous months In this investigation, it was thus found that sudden death was seldom a consequence of labile angina This investigation thus shows that labile angina or diffuse pain in the chest cannot be used as a prodromal symptom to sudden death[20]

Other attempts have been made to calculate the occurrence of sudden death, such as the first manifestation of previously unknown coronary heart disease in the individual—i e , the first and only manifestation in individuals previously free from infarction or angina pectoris Despite varying selection of the populations for investigation and varying diagnostic criteria most of the authors have quoted a figure between 20 and 25 per cent of sudden death from coronary heart disease This is probably due to the fact that the majority of deaths occur during the hours immediately following the onset and that variations in the period of observation thus cause only minor additions to the number of deaths[3,21,28]

In an investigation from Ontario[29] it was concluded that, especially during longer periods of time, sudden death cannot be used as an index of coronary heart disease since sudden death in other diseases can vary considerably at different times This was especially so when the changes in Ontario between *1901 and 1931* were compared with the changes between 1931 and 1951

The importance of environmental factors in sudden heart death

External temperature It is well known that patients with angina pectoris suffer exacerbation in cold weather It has also been shown that in patients with coronary disease, the ECG changes are accentuated when working in cold weather compared to when working in warmer surroundings[30] Gorbatow[31] stated in a review of the literature in 1961 that most authors report higher mortality rates when the external temperature is low while others have not been able to confirm this observation[31] Westlund[2] for example, was not able to confirm this in his studies in Oslo Rose[33] demonstrated correlation between cardiovascular mortality rates and low external temperatures, as Swedish authors have also done[34] In a Swedish study[35] comprising cases of death outside hospital, it was found that there was a correlation between the external temperature and deaths outside the hospital

The hardness of water There are a large number of published observations reporting a connection between soft drinking water and a high mortality rate in coronary heart disease[36-38] Data from Great Britain suggest that the observed correlation is not associated with concomitant socioeconomic factors and that calcium or other factors are the substances in the water which appear to be of importance[39-42] In the above mentioned studies the deaths have not generally been divided up into sudden deaths and other deaths Data from Ontario show that differences in the hardness of water are related to differences in the occurrence of sudden death outside the hospital and that these differences correspond exactly to the differences in total coronary mortality[43,44]

Characteristics for individuals dying suddenly

Prospective studies have demonstrated that sudden death is more common in men than in women and that the occurrence of sudden deaths increases with increasing age[3,26,44-46] The risk factors for sudden death are in general agreement with those for coronary heart diseases generally—i e hypertension, hypercholesterolemia, obesity diabetes cigarette smoking and physical inactivity[3,12,45,49] In the Framingham study hypercholesterolemia and ECG signs of left ventricular hypertrophy were associated with sudden death[25] Cigarette smoking was correlated with death in myocardial

infarction within one hour of the appearance of symptoms but was not correlated with the 3 week mortality rate

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tricular contractions themselves imply an increased risk of sudden death or only constitute another sign of other predisposing factors[11] Pell and d'Alonzo[26] found in another study among the employees of a large company that the very early mortality rate in coronary disease was associated with older age previous hypertension, and ECG anomalies such as disturbances of conduction and premature ventricular contractions

In the 'seven countries study by Blackburn, Taylor and Keyes[60] it was found that the occurrence of premature ventricular contractions at rest detected in the general population (> 10 per cent of the recorded beats) was correlated to the incidence of coronary disease and the mortality rates recorded during the follow up period In this study six concomitant factors were investigated (age skinfold, systolic blood pressure serum cholesterol smoking and the level of physical activity) Premature contractions after working (3 min step test) were not of the same prognostic significance as premature contractions recorded at rest, but the analysis was not complete Hinkle and colleagues[61] used portable ECG recorders in a study of employees of a company During a recording period of six hours the disturbances of rhythm and conduction were recorded in not less than 92 6 per cent of the cases The most common arrhythmia consisted of premature ventricular contractions which were found in 62 2 per cent *In this study too,* the occurrence of ventricular arrhythmias was correlated to findings of coronary heart disease The study confirmed without standardization for concomitant risk factors that the finding of premature ventricular contractions was associated with future coronary death The connection became more pronounced with increasing occurrence of ventricular contractions In Gothenburg too, we have confirmed that there is a connection between premature ventricular contractions and signs of coronary heart disease[62]

None of the studies so far can be considered to have solved the question whether premature contractions in the population are directly or indirectly associated with the phenomenon of sudden death

Studies on infarction patients

Since approximately half of all sudden deaths are directly related to coronary disease, and since more than half of all coronary patients will die suddenly without knowledge of their danger, it is evident that the most effective discriminatory factor concerning sudden death is previous myocardial infarction

Premonitory symptoms in patients with previous myocardial infarction

Progressive angina pectoris so-called "unstable angina, ' has attracted attention as a premonitory symptom[63] It is possible that this symptom is more common prior to infarction or death but angina pectoris itself is a variable symptom Many symptoms noted during the preinfarction period are also common in the general population and the specific discriminatory value of the symptom is not known and at present can not be calculated

In Gothenburg we have at present a group of more than 500 infarction patients below 67 years of age and constituting all hospitalized infarction patients in Gothenburg between 1968 and 1970

Premonitory symptoms in patients with previous myocardial infarction have so far not been specifically studied in the post myocardial infarction clinic in Gothenburg However patients have been in very close contact with the clinic and have received specific instructions to consult the physicians *or nurses if any symptoms* causing them the least concern should occur Almost all of the 38 patients who died suddenly had been in contact with the clinic within one month before dying On retrospective investigation no obvious prodromal signs were detected[64]

At the moment most of the prodromal symptoms are vague not only for the patients but also for the medical profession and therefore fail to activate adequate measures There is no doubt that at the moment extremely little is known about the treatment of unstable angina

High risk groups among patients with previous infarction A prognostic index has been established in order to define groups of infarction patients with varying prognosis[65] Simple factors recorded during

Sub-group I No extensive cardiac damage

Sub-group II Mechanical damage to myocardium

1) Rel heart volume ♂ >450 ml/m² BSA; ♀ >400 ml/m² BSA

2) GPT >40 U during first 3 days

3) BT >38 °C

4) Transient atrial flutter and fibrillation

Sub-group III Electrical cardiac damage

1) VPB frequency >5/min

2) Ventricular tachycardia or ventricular fibrillation

3) AV-blocks a PQ > 0 24 s
b Type II
c Type III

Sub-group IV Combined electro-mechanical damage (Sub-groups II o III)

Fig *1* Criteria for homogeneous sub group allocation of patients 57 to 67 years of age with myocardial infarction Explanation of the schematic is as follows *Sub group I* no extensive cardiac damage *Sub group II* mechanical damage to myocardium (1) relative heart volume (men = > 450 ml per square meter of body surface area women = > 400 ml per square meter of body surface area) (2) glutamic pyruvic transaminase > 40 units during first three days (3) body temperature > 38 C during first three days and (4) transient atrial flutter and fibrillation *Sub group III* electrical cardiac damage (1) ventricular premature beat frequency > 5 *per minute* (2) ventricular tachycardia or ventricular fibrillation and (3) A V blocks (a) P Q interval > 0 24 sec (b) Type II and (c) Type III *Sub group IV* combined electro-mechanical damage (*sub groups II or III*)

every infarction patient s stay in hospital enable a prognosis to be established (Fig 1) [66,67] *The criteria for allocation* of patients to subgroups with regard to risk have been obtained from a previous study on patients in a post *myocardial* infarction clinic in Gothenburg [68] Each single factor was correlated to death as reinfarction during the first post hospital year For convenience the criteria were grouped as follows (1) lack of extensive *cardiac* damage (2) mechanical cardiac damage (3) electrical damage and (4) combined *electro mechanical* damage to the *heart* The presence of isolated criteria is sufficient *for allocation* to a certain group The proportional distribution of the infarction patients and the incidence of death and re infarction in the various groups is shown in Fig 2 Fig 2 also shows the distribution of mortality rate in the groups after an average follow up time of 7 5 months [67]

In the present series of patients discharged from the hospital ventricular arrhythmias occurring during the acute stage are practically always associated with later detected signs of major mechanical myocardial injury (Fig 2) Almost all patients in this series who have had ventricular arrhythmias while in the hospital show signs of myocardial injury

Arrhythmias in patients with previous infarction In total populations in which the prevalence of coronary heart diseases has been low a connection has nevertheless been *demonstrated* between premature

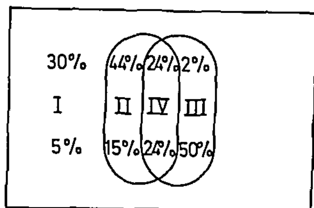


Fig 2 The percentage of patients with myocardial infarction in secondary risk groups (*upper register*) and the rate of reinfarction and mortality (*bottom register*) Average follow up period = 7 5 months

ventricular contractions and coronary disease and also an association between previously recorded premature ventricular contractions and sudden death Furthermore in the group of individuals who have died sudden deaths signs of previous or existing coronary disease have been observed Among patients discharged from the hospital in Gothenburg after myocardial infarction above 57 years of age 77 per cent of the deaths were sudden and below 57 years of age 46 per cent of the deaths were sudden [64]

It is well known that acute ventricular arrhythmias are the cause of the high initial mortality rate in ischemic heart disease Ventricular arrhythmias during the acute stage are correlated to an increase in late mortality rate [68] The incidence of premature ventricular contractions after myocardial infarction was associated with an increased risk of mortality as was shown for the first time among the infarction patients of the Coronary Drug Project [69]

If the period of ECG recording is prolonged 80 per cent of patients have premature ventricular contractions after infarction [70,71] This is therefore not an adequately effective discriminatory factor for sudden death after myocardial infarction The frequency of premature contractions and the circumstances under which arrhythmias occur—e g , physical work—may be of importance [62,72] Various methods of provoking and grading arrhythmias in the infarction patients may enable the allocation of patients to various risk groups concerning sudden death

Conclusions

If primary preventive measures taken before the onset of coronary disease are rewarded with success, it may be expected that this will also reduce the occurrence of sudden death

However it is known that a large number of individuals who later die suddenly have been in contact with a physician during the period immediately prior to dying

The occurrence of sudden death may be expected to be high in a group of myocardial infarction patients discharged from the hospital Every effort to prevent or delay sudden death should be directed at this group in the first place

Our knowledge concerning possible prodromal symptoms and their treatment is at present much too scanty to enable practical recommendations

In view of the present uncertainty concerning the significance of premature ventricular contractions in the chronic stage it is important that controlled studies be performed concerning the ability of various drugs not only to suppress premature ventricular contractions but also to reduce the occurrence of sudden death

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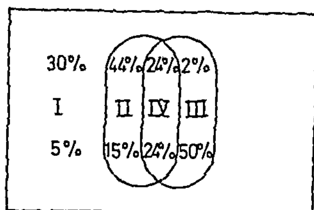


Fig 2 The percentage of patients with myocardial infarction in secondary risk groups (*upper register*) *and the rate of reinfarction and mortality (bottom register)* Average follow up period = 7 5 months

ventricular contractions and coronary dis ease and also an association between pre viously recorded premature ventricular con tractions and sudden death Furthermore in the group of individuals who have died sudden deaths signs of previous or existing coronary disease have been observed Among patients discharged from the hos pital in Gothenburg after myocardial in farction above 57 years of age 77 per cent *of the deaths were sudden and below 57* years of age 46 per cent of the deaths were sudden [64]

It is well known that acute ventricular arrhythmias are the cause of the high initial mortality rate in ischemic heart disease Ventricular arrhythmias during the acute stage are *correlated to an increase in late* mortality rate [68] The incidence of prema ture ventricular contractions after myo cardial infarction was associated with an *increased risk of mortality* as *was shown* for the first time among the infarction patients of the Coronary Drug Project [69]

If the period of *ECG recording is pro* longed, 80 per cent of patients have pre mature ventricular contractions after in farction [70 71] This is therefore not an ade quately effective discriminatory factor for sudden death after myocardial infarction The frequency of premature contractions and the circumstances under which ar rhythmias occur—e g , physical work—may be of importance [62 72] Various methods of provoking and grading arrhythmias in the infarction patients may enable the alloca tion of patients to various risk groups concerning sudden death

Conclusions

If primary preventive measures taken before the onset of coronary disease are rewarded with success, it may be expected that this will also reduce the occurrence of sudden death

However, it is known that a large number of individuals who later die suddenly have been in contact with a physician during the period immediately prior to dying

The occurrence of sudden death may be *expected to be high in* a group of myocar dial infarction patients discharged from the hospital Every effort to prevent o delay sudden death should be directed at this group in the first place

Our knowledge concerning possible pro dromal symptoms and their treatment is at present much too scanty to enable prac tical recommendations

In view of the present uncertainty con cerning *the significance of premature* ven tricular contractions in the chronic stage it is important that controlled studies be *performed concerning the ability of various* drugs not only to suppress premature ventricular contractions but also to reduce the occurrence of sudden death

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Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Drug therapy of heart disease in pediatric patients

I Congestive heart failure in infancy and concepts of developmental pharmacology

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*Eugenie F Doyle M D***
*Monika M Rutkowski M D****
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Etiologic and hemodynamic features of heart failure in infancy

Congestive heart failure in infancy is a common serious pediatric problem The younger an infant is when signs and symptoms of cardiac decompensation occur the worse the prognosis A variety of disease entities may cause heart failure under one year of age (Table I) but by far the leading causes are congenital cardiovascular malformations These are present in approximately 8 of every 1 000 live born infants Thirty per cent of these infants die during the first year of life most of them in congestive heart failure Since these malformations may lead to rapid deterioration of the patient s condition strenuous measures must be employed to treat the cardiac failure diagnose the cardiac defect accurately and refer the patient for prompt surgery if the defect is amenable to palliation or correction

Whatever the etiology of cardiac failure might be the fundamental hemodynamic problem is the same the cardiac output is inadequate for the needs of the body and excessive quantities of blood accumulate in the pulmonic and systemic venous systems A rise in ventricular end diastolic and atrial filling (mean) pressure is the initial response to a drop in cardiac output Subsequently tachycardia widening of the arteriovenous oxygen difference and cardiac dilatation occur The adrenergic nervous system plays an important role in supporting myocardial contractility depletion of catecholamines is associated with increasing manifestation of congestive heart failure

The various congenital cardiovascular defects may cause failure by different mechanisms

Left to right shunts (Group I 1 Table I) There is a volume overload on one or both ventricles in the presence of a large left to right shunt In such a situation ventricular dilatation and tachycardia occur first followed by gradually progressive ventricular hypertrophy There is also an increased

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Left to right shunts (Group 1A Table I) There is a volume overload on one or both ventricles in the presence of a large left to right shunt In such a situation ventricular dilatation and tachycardia occur first followed by gradually progressive ventricular hypertrophy There is also an increased

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with severe iron deficiency anemia When severe myocardial hypoxia persists in such cases myocardial contractility becomes impaired and the severity of the heart failure increases

Clinical features

The onset of symptoms in the infant who is developing congestive heart failure may be rapid and catastrophic as in patients with the hypoplastic left heart syndrome but often is quite insidious

Feeding problems An infant in congestive heart failure may tire after sucking for only a short while He may accept a small amount of milk nap briefly from the exhaustion of sucking and then awaken, crying from hunger This type of feeding history is almost invariably associated with a poor rate of weight gain failure to thrive is usual in infants with heart failure

Tachypnea Heart failure should be suspected when an infant s respiratory rate exceeds 60 per minute in the absence of pulmonary infection or metabolic acidosis since tachypnea is frequently the earliest sign of left heart failure in infancy The respirations in such cases may be labored and are frequently associated with subcostal retractions An expiratory grunt or wheezing may be present Congestion of the bronchial mucosa may cause a chronic cough in some infants and may predispose them to repeated infections Rales are usually heard late in the development of heart failure in infancy and their presence usually indicates that a severe degree of left heart failure exists

Tachycardia A cardiac rate in excess of 150 per minute is almost always present among infants with congestive heart failure A rate in excess of 200 per minute may develop in these patients However in the presence of such a rate one must distinguish between the sinus tachycardia of heart failure and paroxysmal supraventricular tachycardia arising from an ectopic focus In early infancy the latter usually causes a fixed cardiac rate in excess of 250 beats per minute

Cardiac enlargement Cardiomegaly is virtually a *sine qua non* for the diagnosis of congestive heart failure in infancy and the configuration of the enlarged heart is frequently of assistance in diagnosing the underlying cardiac defect Cardiac failure in the absence of cardiomegaly is rare but may be seen when there is infradiaphragmatic insertion of anomalous pulmonary veins into the inferior vena cava or in some cases of cor pulmonale In these instances radiographic changes in the appearance of the lung fields are usually of assistance in making the diagnosis

Hepatomegaly The liver is enlarged and readily palpable in infants with right heart failure When failure develops rapidly the liver edge is rounded and may be quite tender from capsular distension however the liver may be quite hard if the congestion is chronic It is difficult to evaluate the significance of a palpable liver in an infant with pulmonary hyperaeration (e g in the presence of bronchiolitis) since the liver may be displaced downward in such cases by the depressed diaphragm but be normal in size

Sweating and pallor These may be prominent clinical signs in some cases They result from the increased secretion of catecholamines that occurs as the body attempts to maintain compensation

Cyanosis If a patient has cyanotic congenital heart disease (a right to left shunt) e g transposition of the great arteries the cyanosis usually becomes more severe with the onset of heart failure Other patients may develop cyanosis during heart failure due to either decreased oxygen diffusion at the alveolar level or to increased extraction of oxygen at the capillary level

It is not uncommon to see either right or left heart failure in pure form in infants who have congenital heart disease Thus pure left heart failure may occur in cases of coarctation of the aorta and aortic stenosis and marked tachypnea may be the initial sign of cardiac decompensation in such patients On the other hand pure right sided failure with hepatomegaly as the predominant sign may be encountered in the presence of tricuspid valve disease or pulmonic stenosis More commonly however signs of left and right heart failure occur together since a reduction in left ventricular output occurs eventually in all cases This reduced output leads to a diminished renal plasma flow a rise in aldosterone secretion progressive sodium and fluid retention excessive weight gain

Table I. Leading causes of heart failure in infancy

I. Congenital cardiovascular malformations
  A. Large *left*-to-right shunts
    1. Ventricular septal defect
    2. Patent ductus arteriosus
    3. Atrioventricular canal
    4. Total anomalous pulmonary venous return
    5. Truncus arteriosus with increased pulmonary vascular flow
    6. Aortic pulmonary fenestration
    7. A-V fistula (especially cerebral)
  B. Large right-to-left shunts
    1. Complete transposition of great arteries
    2. Tricuspid atresia
    3. Hypoplastic left heart syndrome with patent ductus arteriosus
  C. Obstructive lesions
    1. Coarctation of aorta (usually associated with patency of the ductus arteriosus)
    2. Aortic stenosis
    3. Pulmonic stenosis
    4. Mitral stenosis

II. Endomyocardial diseases
  A. Endocardial fibroelastosis
  B. Myocarditis (especially Coxsackie B)
  C. Cardiac form of glycogen storage disease
  D. Ectopic origin of left coronary artery from pulmonary artery
  E. Medial necrosis of coronary arteries

III. Arrhythmias
  A. Paroxysmal atrial or ventricular tachycardia
  B. Paroxysmal atrial flutter

IV. Circulatory congestion
  A. Overtransfusion or overhydration
  B. Renal insufficiency
  C. Anemia

secretion of norepinephrine which has a direct inotropic effect on myocardial contractility and which increases both systemic vascular resistance and venous tone. When such compensatory measures become inadequate, progressive clinical heart failure results. In infants with large left-to-right shunts, failure most often occurs during the first six months of life.

Right-to-left shunts (Group IB, Table I). In the presence of large right-to-left shunts, severe arterial desaturation results from venous blood shunting directly into the systemic circulation. Thus, in addition to volume overloading of one or both ventricles, these lesions lead to severe hypoxemia which impairs myocardial perfusion and which may lead to severe metabolic acidosis. The acidosis impairs myocardial contractility further and profound heart failure may occur.

Obstructive lesions (Group IC, Table I). These impose an impedance to ejection (systolic overload). The initial compensatory response in such cases is myocardial hypertrophy rather than dilatation. The resultant hypertrophic myocardium requires an increase in total coronary arterial flow. However, there is a greater impairment of flow in subendocardial vessels due to the high intracavity pressure and coronary perfusion may become inadequate for the hypertrophic myocardium. In such cases, depressed S-T segments ("strain pattern") become evident in the precordial leads and congestive heart failure or fatal dysrhythmias may follow.

Endomyocardial diseases (Group II, Table I). These diseases depress myocardial contractility directly. End-diastolic volumes increase as the ventricular ejectile force diminishes and both ventricular dilatation and hypertrophy may become extreme.

Arrhythmias (Group III, Table I). When persistent for more than 24 hours, arrhythmias cause congestive heart failure in the majority of infants affected. The rapid rate of ventricular contraction causes an increase in the coronary blood flow needed to sustain the myocardium. However, the short duration of diastole permits little time for coronary filling and myocardial ischemia eventually occurs. If there is an underlying structural abnormality, heart failure occurs sooner after the onset of paroxysmal tachyrhythmia than when the heart is otherwise normal.

Circulatory congestion (Group IV, Table I). When there is an excessive intravascular volume (diastolic overload) due either to overhydration or severe renal insufficiency, signs and symptoms of congestive heart failure may appear even though the myocardium is ejecting a larger than normal blood volume (high output failure, Group IV). The use of diuretics to reduce the distended venous circulation may be more effective than the administration of cardiotonic agents in such a situation. High output failure may also be seen in association

young infants In this instance the immaturity of their renal function places young infants into a similar category with any patient with renal insufficiency

The activity of the enzyme β glucuronidase in the small bowel of young infants is relatively higher than it is in the intestinal tract of older individuals Since many drugs and other potential toxic substances are excreted in the bile as water soluble glucuronide conjugates the parent compounds (or one of their toxic metabolites) are regenerated when their metabolites undergo hydrolysis catalyzed by this enzyme The resulting compounds are usually quite lipid soluble and are reabsorbed into the systemic circulation This phenomenon of enterohepatic recirculation of compounds that are metabolized to glucuronides renders young infants less able to excrete many potentially toxic substances than older children

It is impossible to apply our current knowledge of the pharmacology of most drugs in such a way that we can predict the immediate or delayed toxic effects of each agent in young infants Thus we have no notion of the effect of various drugs upon the production or distribution of hormones whose actions in the first few weeks of life may be especially critical for the development of an infant s normal intellectual capacity such as thyroxin and insulin Furthermore we are not certain of the safety of barbiturates in the neonatal period since these drugs are highly concentrated within the central nervous system of the young of some laboratory species and remain there for prolonged periods There are many other questions that can be asked about drugs that are used in the newborn period for which no dependable answer can be given However it is possible to avoid the use of drugs that are known to displace bilirubin from its extracellular binding sites when treating young infants It is also possible to exercise care when using agents that may build up within the infant because of his metabolic immaturity and others whose excretion may be slowed by his renal immaturity Certainly physicians who must use pharmacological agents in newborn and other young infants have a right to expect reasonable answers to questions concerning the pharmacology of each new agent in such patients as the drugs are introduced The rapid development of the study of the pharmacology of drugs in the immature and young of many species is new and it will require some time before this expectation can be realized

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and occasionally peritoneal and peripheral edema

Infants with congestive heart failure are at great risk of succumbing rapidly to their disease or to intercurrent infection The prompt institution of therapy to correct their physiological abnormalities is mandatory if they are to survive long enough for a palliative or corrective surgical procedure to be performed If appropriate steps are taken to treat his congestive heart failure even a small premature infant with serious cardiac defects can be salvaged

Concepts in developmental pharmacology

Drugs used to treat patients with cardiovascular disorders alter physiological and chemical processes by interacting at a molecular level with receptors in the various tissues or organs Thus the activity of such drugs is dependent basically upon the nature and number of its effector sites and upon the physico chemical characteristics of the drug itself Since effector sites probably have similar characteristics in most individuals their number and the factors that control the moment to moment concentration of the drug in the body are the important determinants of drug potency and safety The number of effector sites in any given tissue or organism cannot be determined at the present time

The concentration of a drug in the body at any point in time is determined by a complex set of kinetic constants that describe its absorption distribution metabolism, and excretion These constants vary not only with the nature of the drug and its route of administration but also with numerous intrinsic host factors Thus host factors play a major role in controlling the net amount of drug in the body at any time These factors include the patient s size the other drugs he is taking the nature of his disease his genetic endowment and his physiological maturity

The current interest in developmental pharmacology is the direct result of untoward occurrences that followed the use of drugs in young infants without regard for the added hazards to them imposed by immaturity of the systems that control drug distribution, metabolism, and excretion Some of these are summarized below

Distribution All newborn infants develop some degree of hyperbilirubinemia during the first several days of life The distribution of bilirubin in the body is controlled to a great extent by the number of binding sites available for it on the plasma albumin In most cases, the distribution of the pigment is such that the cells of the central nervous system are not affected by its cytotoxic action However, when the albumin is not capable of maintaining this favorable equilibrium serious brain damage and even death may result Thus the use of such bilirubin displacing drugs as the antibacterial sulfonamides the sulfonamide diuretics and strong acids (e g ethacrynic acid) is contraindicated during the hyperbilirubinemic stages of early life

Metabolism Most of the enzymatic reactions that convert drugs into their various metabolites in the body are catalyzed at a slow rate in young infants Agents that require extensive metabolic alteration before they are eliminated must therefore be given to such patients in adjusted doses Failure to recognize this can result in the accumulation of active drug within the body and can lead to serious toxicity When chloramphenicol was administered to newborn infants in usual doses (adjusted only for the infant s weight) many infants developed the gray syndrome and died It is now known that this syndrome of abdominal distension respiratory distress and circulatory collapse associated with a peculiar grayish color to the skin is related to the toxic effects of extremely high concentrations of the active drug in the body It occurred in young infants because chloramphenicol is an antibacterial agent which requires metabolic alteration before it can be excreted and which built up in the infants due to their inability to convert it to its less toxic excretable metabolites The ' gray syndrome was avoided in later years by adjusting the dose of chloramphenicol for the infant s metabolic immaturity as well as for his size and weight

Excretion Renal blood flow glomerular filtration and tubular function are all diminished in young infants Accordingly drugs that are excreted unchanged in the urine, or those whose water soluble metabolites may be toxic in high concentration, must be administered with great care to all

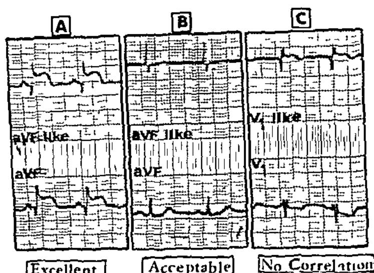


Fig. 1 Examples of the degree of correlation in simultaneously recorded conventional lead (*lower tracing*) and monitoring lead (*upper tracing*) ECG See text for explanation

and shape of QRS and P waves though the complexes were not identical *No correlation* describes no similarity in form and/or direction (Fig 1) In the V_1 like lead *excellent correlation* was found in 52 patients (86 6 per cent) *acceptable correlation* in 7 (11 6 per cent) and *no correlation* in only 1 case (1 7 per cent) *Excellent correlation* was present in 49 patients (81 6 per cent) with the aV_F-like lead *acceptable correlation* in 9 (15 per cent) and *no correlation* in 2 (3 4 per cent) In the cases in which *no correlation* was found the QRS complex in the conventional lead was always isodiphasic thus probably explaining why small changes in the electrode position resulted in significant differences in the shape of th complexes recorded by the monitoring lead

The almost insignificant number of patients in whom lack of correlation was found when comparing monitoring and conventional leads confirms the postulate that the ba ic diagnostic conclusions derived from the conventional ECG can be safely and reliably applied to the features obtained in a properly placed b polar chest lead

In setting up a continuous ECG monitoring system the adoption of a standard method of electrode placement seems advisable since such a method allows easier interpretation of ECG data by the unit s staff and provides adequate information for more sophisticated computerized systems of arrhythmia detection as well

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Natural history of childhood lipoid nephrosis

Recent studies have shown that the vast majority of children with the nephrot c syndrome have minimal histological changes by renal biopsy This type of renal d sease var ously termed "nil disease epithelial cell disease and lipoid nephrosis is characterized by complete remissions induced by glucosteroid therapy Sixty one children with the nephrotic syndrome defined by heavy proteinuria hy

Annotations

A sign of cardiac arrest

The physician is frequently confronted with a patient who complains of suddenly losing consciousness. When seen by his physician the patient fails to display signs or symptoms which make it possible to establish the cause. As a result the diagnosis is not established and management is unsatisfactory. Such patients are often considered to have a Stokes Adams attack whereas other patients are told that they have experienced a simple fainting or syncopal episode. However careful history taking from the patient and from anyone who has observed him faint can provide important and almost diagnostic information. The patient who suddenly develops unconsciousness due to cardiac arrest often experiences a generalized flushing and warmth or burning and tingling sensation of the skin of the entire body. He develops a marked redness or blush due to vasodilatation of the veins and other vessels of the skin and then suddenly falls unconscious. Careful questioning of the patient when he recovers from cardiac arrest or Stokes Adams attacks will often reveal this fairly characteristic syndrome. On the other hand patients with the common forms of syncopal episodes gradually or relatively slowly become extremely pale to ashen gray, sweaty, weak, giddy and then faint. They do not display the manifestations noted above for sudden cardiac arrest.

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Standard monitor leads— As reliable as conventional leads?

Two leading articles in the field of cardiac arrhythmias[1,2] have recently re-emphasized the need for a uniform lead system in continuous electrocardiographic (ECG) monitoring. Doctors and nurses trained in the interpretation of the conventional ECG are often unable to make a diagnosis when dealing with an arbitrarily placed bipolar chest lead, and immense quantities of ECG information are overlooked in thousands of patients being monitored daily. In addition the introduction of more automated methods of arrhythmia detection require standard ECG data which can feasibly be converted into simple computer programs.

In an attempt to overcome the limitations of arbitrarily placed electrode, Marriott and Fogg[3] described a set position which permits recording of a lead closely resembling the conventional V_1 lead. A modification of this method was suggested,[4] which likewise produces a V_1 pattern that can be easily changed into an aV_F pattern without altering the position of the chest electrodes on the patient.

We believe that more and more Coronary and Intensive Care Units will adopt one of these systems and comparable standard tracings will then be available in an increasing number of patients.

The question arises to what extent do the electrocardiographic features of the monitoring leads conserve the diagnostic implications of the conventional ECG leads.

We tried to find the answer to this question by recording parallel data in 60 consecutive unselected patients and evaluating the degree of correlation between the monitoring and the conventional leads. The conventional and the monitoring leads were simultaneously recorded on a two-channel recorder (Sanborn 7212) equipped with 2 ECG pre-amplifiers. Chest electrodes were placed as previously described.[4] Briefly, electrode I was placed at the usual V_1 position, electrode II was placed below the outer third of the left clavicle, and electrode III was placed at the left anterior axillary line over the ninth to tenth intercostal space. When electrode I is positive, II negative, and III ground, a V_1-like lead is recorded. If electrode I is connected to the ground wire and III to the positive pole, an aV_F-like lead is recorded.

The results were tabulated as follows: an *excellent* correlation describes the situation where all the details of the ECG were identical. An *acceptable* correlation refers to a similarity in direction

three all had persistent proteinuria two had mildly elevated BUN (20 and 30 mg per 100 ml respectively) and serum creatinine (2.7 and 3.0 mg per 100 ml respectively) and the remaining patient had an elevated blood pressure (150/100 mm. Hg). Four patients had died three of these were steroid resistant and had renal insufficiency at the time of death the fourth was steroid responsive and died of fluid and electrolyte complications during a relapse

These data indicate that the nephrotic syndrome in preschool age children is not a benign disease despite the high responsiveness to treatment and the nature of the histologic lesion. Although the incidence of progression to renal failure remains low and for most children there is a marked reduction in the frequency of relapses by the time they reach adolescence recurrences will be experienced by the majority of patients for many years

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The distress of dying

In contrast to many subjective reports few objective assessments [1] have been made on the distress of dying. Doctors spend little time with dying patients so the observations recorded by nurses can be of particular value in providing a more comprehensive assessment than most doctors make alone. For this reason charts were devised that enable nurses to record the distress of dying in a manner similar to their recording of temperature (TPR) charts

The factors to be assessed include pain respiratory distress at rest awareness of dying depression anxiety vomiting and incontinence. Pain is recorded on a vertical chart graded 0 to 10 with the absence of pain recorded as 0 and very severe pain as 10. A similar principle is used for recording the other features of distress. The chart provides a useful pictorial image the significance of which is easily assessed. In extracting data for statistical analysis one has the problem of taking and analyzing from diurnal linear charts information recorded in a manner similar to that normally used for temperature chart. One can take the highest lowest or average figures though where the aim is to relieve distress the highest figures are most important and these are the ones used

Data was obtained about 50 consecutive deaths occurring at home or hospital during a 12 month period in the Llanidloes area of Wales. Significant differences occurred between deaths at home and in hospital for three reasons. Patients dying at home were (1) more likely to be fully alert shortly before death (P < 0.05) (2) less likely to be suffering from vomiting incontinence or bedsores (P < 0.001) and (3) less likely to have unrelieved physical distress (P < 0.05)

It is possible that the presence of an alert mind and the absence of symptoms requiring constant nursing care determined the site of death of these patients. Most people dying at home were free from vomiting incontinence and bedsores whereas 28 per cent of all patients were troubled at some time by vomiting 30 per cent had bedsores 30 per cent had fecal incontinence 2 per cent a colostomy 20 per cent required an indwelling catheter and another 46 per cent had urinary incontinence. Only 26 per cent had none of the above symptoms

Twenty two per cent revealed an awareness that they might die 10 per cent expected to die soon 10 per cent thought they would probably die and 2 per cent thought they might possibly die. Fifty four per cent experienced pain of varying severity and 26 per cent had severe or very severe pain. Only 20 per cent had no respiratory distress at rest 26 per cent had severe or very severe respiratory distress though in some of these instances the respiratory distress was mitigated by the fact that they were stuporose or comatose. Fifty six per cent experienced some anxiety and 40 per cent had depression. At times the anxiety of 14 per cent was so severe they could be described as fearful

The results can be compared with those reported by Hinton[1] and Exton Smith[2] though the three surveys did differ in method type of patient studied and environment. In Llanidloes consecutive deaths in a community were assessed by trained nurses. The 220 patients in Exton Smith's survey[2] all died in a geriatric unit. His information was obtained from personal observation and close enquiry from the nursing staff. Hinton's study was confined to a teaching hospital. He interviewed 102 dying patients and later questioned the sister or staff nurse about the state of the patient in the last few hours of life. On average the oldest patients were in Exton Smith's group[2] and the youngest in Hinton's.[1]

The cause of death differed in the three surveys

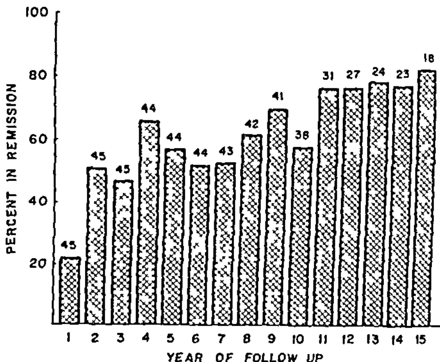


Fig *1* The percentage of the relapsing group in complete remission during each year of follow up is shown by the bar and the number of patients remaining in the group is indicated at the top of each bar

poalbuminemia and edema and who had no known etiology for their disease formed the basis of our report [2] Clinical criteria u ed in selecting these patients were minimal follow up period of 5 years age of onset 12 to 72 months and complete remission due to initial steroid therapy White and colleagues[1] have demonstrated that these clinical characteristics will define a homogenous group of patients with lipoid nephrosis Follow up was 10 years for 51 patients 15 years for 21 patients and the average period of observation was 13 7 years

There were 10 patients who experienced only the initial episode and 51 patients who had one or more recurrences There were 47 boys and 14 girls and the mean age of onset was 37 months Clinical features during the initial episode such as hematuria transient hypertension and azotemia were not helpful in predicting whether an individual patient would follow a relapsing or non relapsing course The most helpful feature in determining the likelihood of a relapsing course was the duration of remission after the initial episode Twenty two patients were without relapse during the first year after onset and of these 12 (55 per cent) subsequently had at least one relapse Of the 13 patients who were in remission during the first two consecutive years from onset 23 per cent subsequently relapsed while only one of eleven patients without relapse during the first three consecutive years had a later recurrence All 10 patients who did not relapse during the first four consecutive years after onset remained in remission until the end of follow up These data suggest that the relapsing form of lipoid nephrosis is evident during the first two years of the disease and that complete resolution or cure is likely in the absence of a recurrence during the first three years after onset In contrast to patients with a non relapsing course once a patient had experienced even one relapse the likelihood of predicting complete resolution even after extended periods in remission was uncertain For example of 31 patients in remission for five years at some time during the course of illness after a relapse seven (22 per cent) subsequently had a recurrence

Sufficient data were available on 45 of the 51 cases with a relap ing course for long term evaluation of the frequency and pattern of relap es While only 23 per cent remained free of relapse during the first year approximately one half of the group was in remis ion during each of the subsequent six years Although the proportion in remission gradually increased with time 20 per cent of the group had relapses as long as 15 years after onset (Fig 1) Similarly during the first year after onset the group averaged more than one relapse per patient but thereafter the relapse rate was less and a distinct trend toward a decreasing rate was evident after the tenth year of disease

The clinical status of all 61 patients at the end of the study was evaluated by complete history physical examination urinalysis blood urea nitrogen (BUN) and serum creatinine The ten patients who had only the initial episode each had a normal BUN serum creatinine and blood pressure at the completion of follow up Of the 51 patients with a relapsing course 25 had been in remission for a minimum of two consecutive years 22 were continuing to experience relapses 13 of these were steroid responsive 6 were steroid dependent and 3 were steroid resistant Of these 47 patients all had normal BUN serum creatinine and blood pressure except the three who were steroid resistant Of these

Letters to the Editor

Lidocaine in ventricular arrhythmia

To the Editor

Lidocaine is considered to be the drug of choice in the initial treatment of ventricular arrhythmias especially during an acute myocardial infarction Electrophysiologic studies by Rosen and co-workers[1] using a single bolus of lidocaine and Josephson and co-workers[2] using a bolus of lidocaine followed by an intravenous drip of 1 mg per minute demonstrated no significant effect on A V nodal or His-Purkinje conduction time in man The recent article by Josephson and colleagues on the effects of lidocaine on refractory period in man observed the development of complete A V nodal block with ventricular asystole in one patient followed by persistent delay in His-Purkinje system conduction upon return to normal sinus rhythm [2] We have recently observed a similar patient who developed asystole and complete heart block following a bolus injection of lidocaine

A 49 year-old Caucasian male physician weighing 140 lbs sustained an anterior wall infarction complicated by a right bundle branch block left anterior hemiblock myocardial aneurysm and congestive heart failure in December 1971 On December 9 1972 he was admitted to the C C U with a chief complaint of severe crushing substernal chest pain of several hour duration His medications consisted of digoxin 0 25 mg and Esidrix 50 mg daily His initial serum K^+ was 4 1 mEq Because of frequent premature ventricular contraction and short runs of ventricular tachycardia 80 mg of lidocaine was rapidly administered as a bolus intravenously Within 2 minutes complete heart block with ventricular asystole developed atrial activity however was not affected Immediate closed chest massage and ventilation were initiated and ventricular escape beats emerged (Fig 1) Within 10 minute regular sinus rhythm returned A temporary pacemaker was then inserted to allow the use of continued antiarrhythmic medication—lidocaine The patient died on the third hospital day following the development of refractory ventricular arrhythmias

This experience would seem to be the second documented episode of ventricular asystole following the administration of lidocaine We have previously reported the occurrence of sinoatrial arrest as a complication of lidocaine[3] In the present case lidocaine may have depressed conduction through the posterior division of the left bundle We concur with the conclusions of Josephson and colleagues[2] that smaller than average doses of lidocaine be administered to patients with congestive heart failure or liver disease of any etiology In the presence of bilateral bundle branch block lidocaine should probably be administered with caution and slowly

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Atrial dissociation

To the Editor

In the latest case report of Atrial Dissociation by Drs Sivertssen and Jorgensen (AM HEART J 85:103 1973) it appears that an entirely different interpretation can be made of the electrocardiogram the intracavitary electrogram and the alleged atrial activity

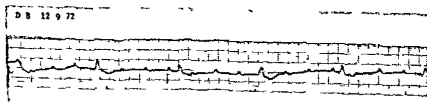


Fig 1 Monitor strip showing complete heart block Ventricular rhythm = 37 per minute atrial rhythm = 125 per minute

mainly because 80 per cent of Hinton's patients died from cancer. He reported that discomfort was not greatest in patients dying from cancer but patients dying from heart failure or both had most physical distress.[1]

Hinton also pointed out that an awareness of dying increases as death draws closer: 75 per cent of his patients indicated such an awareness during the final weeks. The Llanidloes figure of 22 per cent is much lower, probably because the nurses did not seek this information but recorded only information volunteered by patients. It is similar to the 25 per cent reported by Exton Smith,[2] so from these two studies it seems likely that about a quarter of dying patients indicate an awareness of approaching death to their attendant nurses. Three and two-tenths per cent of Exton Smith's patients[2] and 10 per cent of those in Llanidloes expected to die soon, while the figures given by Hinton[1] range from 6 per cent at the first interview to 20 per cent during the last week of life.

Impairment of consciousness increases as death approaches: 34 per cent of Hinton's patients[1] were unconscious for at least 24 hours before death and 40 per cent of those dying in Llanidloes were in the same state.

Thirteen and six tenths per cent of Exton Smith's patients[2] experienced moderate or severe pain. Hinton[1] found that 65.7 per cent had pain, though the severity was not classified, and 18 per cent of those with pain failed to receive adequate relief. In Llanidloes 54 per cent had pain with 26 per cent experiencing severe or very severe pain. Hinton[1] stated that dyspnea is more difficult to relieve than pain, nausea, or vomiting and that out of 17 patients suffering from respiratory distress 14 (82 per cent) failed to obtain relief.

A few patients (3.2 per cent) in Exton Smith's study[2] showed severe anxiety and were afraid to be left alone. Hinton[1] found that 64.7 per cent showed at least slight anxiety and 12.7 per cent experienced moderate anxiety, but none were classified as fearful. In Llanidloes 56 per cent showed at least slight anxiety, while at times 14 per cent were fearful. Hinton[1] included as severely anxious or fearful only patients who had been fearful, agitated, or panic stricken for most of the week. In Llanidloes any transient state of fearfulness that the nurse noted was included. Depression occurred in [illegible].7 per cent of Exton Smith's patients,[2] while Hinton[1] found that 66.7 per cent experienced some depression and that 16.7 per cent experienced moderate or severe depression. In Llanidloes 40 per cent experienced at least slight depression, while 26 per cent were moderately or severely depressed. Altogether, 12 per cent of the Llanidloes patients wanted to die, which is higher than the 5 per cent reported by Exton Smith.[2] Hinton[1] pointed out that 65 per cent of depressed and 52 per cent of anxious patients remain unrelieved.

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by Dr Oriscello Dr Chien and Dr Màdàrang However we do not agree with their interpretation of the electrocardiograms

First the waves which we interpreted as right atrial activation with A V dissociation occurred at the rate of 105 per minute (paper speed 50 mm per second) These waves could clearly not be due to diaphragmatic electrical activity The morphology in intracavitary lead from different parts of the right atrium in our opinion excludes any other possibility than that of a right atrial P wave

Second we are not convinced that our identification of the QRS complex is wrong Recordings from the distal part of the right atrium close to the tricuspid valve which was not published in our paper strongly suggest that the largest waves seen in Lead V_1 are QRS complexes Additional support to our interpretation is found in our present Fig 1 which shows another strip of the electrocardiogram A slightly irregular rhythm is seen with one premature beat The relation between what we interpret as the P wave and the QRS complex is constant except in the beat following the premature beat when the PR interval is slightly shortened However the correct identification of the P and the QRS complexes is not essential for the diagnosis of atrial dissociation if our interpretation of the extra right atrial P wave is accepted

Discussing the interpretation of the electrocardiogram yet another alternative deserves mentioning namely the possibility that both waves belong to the QRS complex—i e gross intraventricular conduction disturbance is present The ECG should then be one with atrioventricular dissociation and intraventricular conduction defect However we do not feel that this is the correct interpretation

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In Fig 1 the initial PR interval is about 0 24 second The ST segment is elevated in V_1 and V_2 This appears to be an acute anteroseptal infarction with an old inferior infarction The PR prolongation suggests severe septal damage Notice appropriately the QRS is followed by a T wave

In Fig 2 what is identified as a QRS complex is not followed by a T wave Therefore this is probably the P wave What was identified as the P wave is the QRS complex Notice the large S in LI with left axis deviation It is now apparent that what was identified as a P wave in V_1 is found to be a QRS complex with an RSR pattern The PR interval would now be about 0 54 second or more further prolonged over what was initially seen rather than being shortened as suggested by the authors interpretation There is little doubt that this is trifascicular block The acute anterior wall infarction is demonstrated by the loss of precordial R wave with ST segment elevation The T wave is lost in the P wave The giant P waves suggest severe pulmonary hypertension It is of interest to speculate that the elevated PR segment in Leads I aV_R aV_L and V_4 through V_6 with PR segment depression in Leads II III aV_F V_1 and V_2 may represent atrial hypertension and atrial infarction

If one carefully measures what is taken as an extra P wave in the right precordial lead and the atrial electrogram (again the P wave and the QRS misidentified) it is at the rate of about 50 per minute If one were to refer back to the nurses notes, tachypnea at this rate would be described

What one is seeing is diaphragmatic electrical activity that we have described[1] as a preterminal sign in severe obstructive lung disease or congestive failure when severe hypoxia is present

It is not uncommon to mistake diaphragmatic action potentials for dissociated atrial activity We hope that the re review by the authors is in agreement with us

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Reply

To the Editor

We appreciate very much the interest in our case report of atrial dissociation and the comments made

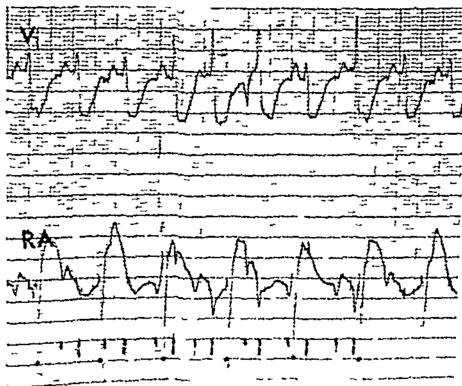


Fig 1 Electrocardiogram showing Lead V_1 and intracavitary right atrial (*RA*) lead A close time relationship is found between the waves which are interpreted as P waves (marked) and those interpreted as QRS complexes (marked)—but not in the opposite direction—in spite of irregular rhythm Independent of these waves large negative complexes (marked) are seen in the RA lead interpreted as right atrial P waves Paper speed = 25 mm per second

perform diagnostic wonders at the bedside This book should interest all students interns and residents as well as doctors in practice who wish to become proficient in examination of the heart This is a valuable publication

√SPONTANEOUS HYPERTENSION Its Pathogenesis and Complications Edited by Kozo Okamoto M D Tokyo 1972 Igaku Shoin Ltd 266 pp Price $24 80

Dr Okamoto s book contains the papers presented at a seminar held in Kyoto from October 18 to 22 1971 on a strain of rats that develop hypertension spontaneously Investigators from many parts of the world who are studying various aspects of this syndrome in the rats participated in the conference This publication consists of 8 chapters Several papers are included in each chapter The subjects discussed were development and heredity catecholamine metabolism neural factors and behavior cardiovascular dynamics cardiovascular pathology endocrine factors renal factors and electrolytes and essential hypertension and spontaneous hypertension These presentations of this interesting phenomenon extensively review the pathophysiology of an interesting d sease and animal model of hypertension Regardless of its relationship to hypertension in man this book is an extremely important one The seminar gathered together a great deal of valuable information for others who are interested in hypertension This is an important publ cation

√CEREBRAL VASCULAR DISEASES Eighth Conference Flet her H McDowell M D Chairman and Fletcher H McDowell M D and Robert W Brennan M D Editors New York 1973 Grune & Stratton Inc 319 pp Price $12 50

The publication of the proceedings of the Eighth Conference on Cerebral Vascular Diseases reflects a meeting which resembles the preceding ones This book contains discussions of extracranial arterial surgery and a preliminary report on the cooperative aneurysm project various aspects of cerebral ischemia (pathology microcirculation metabolism pathophysiology) head injuries cerebral angiography role of platelets and pharmacology The papers are interesting and the appended discussions are even more important to readers who were not in attendance at the conference This is another important publication which should interest all physicians not only neurologists and neurosurgeons

√ESSENTIALS OF CARDIAC ARRHYTHMIAS Diagnosis and Management Samuel Bellet M D Philadelphia 1972 W B Saunders Company 458 pp Price $15 50

This book of 38 chapters on one of the most important problems in cardiology was written by Dr Bellet shortly before he died of myocardial infarction He had been interested in arrhythmias of the heart for many years and has written fairly extensively on the subject As in previous writings th s book is intended for the practicing physician It is well organized and clearly written The 38 chapters cover all the common arrhythmias and their management as well as the anatomic and physiologic considerations necessary for an understanding of the arrhythmias This is a well illustrated book and a good addition to the many others already available on the subject Students interns and residents will find the book to be useful

Book reviews

ADVANCES IN MICROCIRCULATION Vol 4 H Harders editor Hamburg Basel New York 1972 S Karger AG 232 pp Price $24 40

This fourth volume on Advances in Microcirculation should interest all physiologists and all physicians who treat cardiovascular diseases It is divided into six parts related to microcirculatory blood flow hemodilution and rheologic changes effects of dietary fats plethysmography thermography use of radionuclides labelled colloids and leukocyte sequestration in the pulmonary circulation in hemorrhagic shock As are the past volumes this is also a very good one The reader will find this book to be interesting and useful it is highly recommended

RECENT ADVANCES IN RENAL PHYSIOLOGY Editors H Wirz and F Spinelli Basel 1972 S Karger AG 298 pp Price $27 45

This publication contains papers presented at an international symposium held in Brestenberg Switzerland August 2 to 5 1971 The sessions were concerned primarily with the handling of sodium by the kidneys The many papers were related to mechanisms of sodium excretion renal circulation function of the medulla and diversity of the nephrons The contributors have studied water and electrolyte excretion rather extensively and gathered as in all such symposia to exchange views and findings This gathering must have been interesting as reflected in the resultant publication Those who are interested in the fundamentals of renal function will find this book to be stimulating and useful The papers are thought provoking in that they readily reveal the many questions yet to be answered Renal physiologists will find this to be a valuable publication

ANGINA PECTORIS American Heart Association Monograph No 37 Edited by Charles K Friedberg M D with the assistance of Ephraim Donoso M D New York 1972 1 227 pp Price $5 00

The American Heart Association has for the past several years published symposia on various important cardiologic problems This is the thirty seventh on an extremely important clinical state which waxes and wanes in interest among clinicians At present it is of considerable interest because of the surgical approaches to the management of coronary heart disease This publication contains nothing new to cardiologists but it should interest others who fail to follow the medical literature closely The subjects discussed are of routine interest though important—viz coronary angiography bypass surgery medical management diagnosis This monograph should interest students young physicians internists and general practitioners

NEURAL AND PSYCHOLOGICAL MECHANISMS IN CARDIOVASCULAR DISEASE Proceedings of a Symposium held in Stresa Italy July 19–21 1971 Edited by Alberto Zanchetti Milano 1972 Casa Editrice 387 pp Price $25 00

These proceedings of an excellent symposium held in Stresa Italy July 19 through 21 1971 on the psychological factors in cardiovascular disease should be welcomed by those who were unfortunate not to have been present at the sessions Among the many subjects discussed were those related to methods for evaluating neural and psychologic factors in cardiovascular disease influence of personality and perspectives The many interesting presentations were delivered by contributors from many parts of the world The book is very good and reflects outstanding work of the organizing group from Milano This is an important and interesting contribution to the medical literature The series of papers should interest all physicians

PHONOCARDIOLOGY Integrated Study of Heart Sound and Murmurs Jozef Wartak M D New York 1972 Harper & Row Publishers 156 pp Price $17 50

The short monograph on heart sounds is a little different from the usual publications The author presents the physics of sound in a simple fashion He does this with good clear illustrations which the reader must study carefully The relationship of heart sounds to other hemodynamic and to electrocardiographic phenomena is illustrated These illustrations require thoughtful study and understanding The normal and abnormal heart sounds and murmurs are well presented The author refrains from discussion of controversial matters This is a good idea for a book of this type The book is useful for beginners

AUSCULTATION OF THE HEART 4th ed By R W D Turner Edinburgh 1972 Churchill Livingstone 122 pp Price $5 50

This small paperback on examination of the heart is not only an important and practical publication but a much needed one in this era of the cardiac catheter A well trained cardiologist can

Announcements

Appeal for rheumatic subcutaneous nodules

An appeal is made to physicians and investigators for rheumatic subcutaneous nodules recently formed in the course of rheumatic carditis for use in studies on the pathogenesis of rheumatic fever

Nodules situated on the extremities readily accessible to biopsy and just in the process of forming before steroid therapy are especially sought, although any nodules will be welcome Self addressed containers with fluids and details concerning biopsy technique may be obtained from Dr Bernice G Wedum c/o Mr Gun Hyuk Kim Bldg 37 Room 1C27 National Institutes of Health Bethesda Md, 20014

adverse actions can be terminated by stopping administration or rarely by the administration of propranolol

A more serious toxic effect has been described for i oproterenol myocardial infarction and necrosis This occurs in experimental animals to which massive doses of isoproterenol have been given The doses needed are at least 1 000 times larger than any therapeutic dose And thi effect is produced by any active catecholamine This tissue damage is probably due to phys ical effects of intense myocardial stimulation relative coronary insufficiency and direct biochemical effects of the catechol amines There is no evidence that this adverse result can or has happened with any therapeutic or diagnostic use of isoproterenol

Are there any drug interactions to worry about when using isoproterenol? Obviously *beta* blocking agents would interfere in the use of isoproterenol in bronchial asthma However *beta* blockade is a property of a fairly restricted chemical structure Veratrum alkaloids would diminish the positive chronotropic action of isoproterenol However drugs that interfere with adrenergic transmission such as reserpine guanethidine methylphenidate or cocaine would not affect the isoproterenol response This catecholamine not being significantly taken up by the amine pump of the nerve end is not affected by denervation phenomena

Isoproterenol should be the drug of choice whenever the effect of specific sympathetic nerve stimulation of the heart is de ired This conclusion is valid only at the present instant in time There are indications that the cardiac *beta* receptors are different from smooth muscle *beta* receptors Cardioselective *beta* blocking agents are undergoing clinical trial now It won t be long until cardioselective *beta* agonists will be readily available At that time our opinion of the use of isoproterenol may have to be changed

terenol is unquestioned There are *only two* questions is a decongestant action *needed* also (by substituting epinephrine or *adding* phenylephrine), and how *should the iso*proterenol be administered? The latter question arises for any clinical use *of iso*proterenol As a catecholamine its survival when administered orally is *extremely* variable When first tested clinically *in this* department in the 1940 s, *isoproterenol* was supplied as an oral tablet This, however, was most unsuccessful *Some subjects* showed no response others showed extreme tachycardia and palpitations

Three methods of administration are available intravenous infusion for prompt, *controllable* cardiovascular effects sub*lingual or buccal* tablets for chronic sys*temic action* and *inhalant* solutions for *local action in the* bronchi

The *syncope of complete* heart block is due to low cardiac output caused by epi*sodes of either brady*cardia or ventricular fibrillation Unless the ECG is being con tinuously monitored *it may be difficult* to distinguish which *condition is present* Isoproterenol is the drug *of choice it will correct* bradycardia and there is reasonable *evidence that it would* not *prolong* a short episode of fibrillation Transient *complete* heart block is readily *treatable with iso*proterenol Permanent heart block *is usually treated by* pacemaker implantation

The use *of isoproterenol* in cardiogenic shock is more uncertain The *hypotension* and weak pulse associated with *pulmonary* embolism open heart *surgery or acute* myocardial infarction is *presumed to be* due to myocardial weakness On this basis a rapid acting positive inotropic agent is indicated This can be either isoproterenol or norepinephrine Both agents affect the cardiac *beta* receptors to increase the force of contraction and improve cardiac output Norepinephrine by adrenergic *alpha* recep tor action can produce in addition vaso constriction and a pressor response Iso proterenol will tend to increase pulse rate norepinephrine will tend reflexly to de crease pulse rate Isoproterenol will tend to increase coronary flow, but by decreasing total peripheral resistance may adversely affect renal and cranial blood flow Norepi nephrine, while increasing coronary flow by *beta* receptor action and by increasing arterial pressure by *alpha* action may be more seriously producing renal shutdown *And finally* both drugs can produce serious *arrhythmias It* should be noted that in experimental pharmacology an easy way *to produce arrhythmia* is simultaneous *stimulation of the* vagus and sympathetic nerve supply of the heart

It seems obvious then that the choice of drug depends on the exact conditions in each patient being treated This is shown by the clinical literature on the subject, success and failure for each drug isopro*terenol* and norepinephrine is well docu*mented*

In many ways isoproterenol should be of great value in cardiology Administered intravenously its actions are predictable and controllable Two examples of the experimental and diagnostic value of iso*proterenol* can be cited

Many clinical studies of new and old adrenergic *beta* receptor blocking agents are being done at the present time Any drug action purporting to be due to beta receptor blockade must be proved by com parison of the subject s response to iso proterenol before and after the experi mental drug dosage Isoproterenol acti vates all *beta* receptors so it can be used as a control for any *beta* blocking agent includ ing the newer cardioselective agents such as practolol Without this control other ac tions of the experimental drug may be producing the observed effect

Isoproterenol increases the functional stenosis in idiopathic hypertrophic sub aortic stenosis This action has value during diagnostic and evaluative catheterization Unfortunately the converse of this effect is not true adrenergic *beta* receptor blocking agents are not often beneficial in this form of stenosis

Is isoproterenol a safe drug? As with any drug too much can be administered In any reasonable 'therapeutic overdosage only two adverse things can happen tachy cardia and relative coronary insufficiency Isoproterenol is less likely to produce severe arrhythmia than either epinephrine or norepinephrine The coronary insufficiency is due to the disparity between the increased coronary flow and the even greater in creased myocardial oxygen demand caused by the intense myocardial sti lation The

adverse actions can be terminated by stopping administration or rarely by the administration of propranolol

A more serious toxic effect has been described for isoproterenol myocardial infarction and necrosis This occurs in experimental animals to which massive doses of isoproterenol have been given The doses needed are at least 1 000 times larger than any therapeutic dose And this effect is produced by any active catecholamine This tissue damage is probably due to physical effects of intense myocardial stimulation relative coronary insufficiency and direct biochemical effects of the catecholamines There is no evidence that this adverse result can or has happened with any therapeutic or diagnostic use of isoproterenol

Are there any drug interactions to worry about when using isoproterenol? Obviously *beta* blocking agents would interfere in the use of isoproterenol in bronchial asthma However *beta* blockade is a property of a fairly restricted chemical structure Veratrum alkaloids would diminish the positive chronotropic action of isoproterenol However drugs that interfere with adrenergic transmission such as reserpine guanethidine methylphenidate or cocaine would not affect the isoproterenol response This catecholamine not being significantly taken up by the amine pump of the nerve end is not affected by denervation phenomena

Isoproterenol should be the drug of choice whenever the effect of specific sympathetic nerve stimulation of the heart is desired This conclusion is valid only at the present instant in time There are indications that the cardiac *beta* receptors are different from smooth muscle *beta* receptors Cardioselective *beta* blocking agents are undergoing clinical trial now It won t be long until cardioselective *beta* agonists will be readily available At that time our opinion of the use of isoproterenol may have to be changed

Clinical communications

Changes in the coronary vasculature in endomyocardial fibrosis and their possible significance

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In the first study of the pathology of endomyocardial fibrosis that was published by this Department[1] a striking vascular lesion was described in one of the four cases presented. That lesion was interpreted as consisting of thrombosis with organization and recanalization. It involved medium sized and small arteries in the fibrotic endomyocardial areas. Other but less impressive changes, such as medial fibrosis and intimal thickening, were seen in all the other cases. As further cases of endomyocardial fibrosis have come under microscopic observation there has emerged what in our opinion seems to be a peculiar pattern of vascular changes affecting the coronary vessels in this disease.

Although the gross and histological features of the heart itself have been thoroughly studied in cases of endomyocardial fibrosis,[2-6] little attention has been paid to changes in the coronary vessels, specially those of smaller caliber. Moreover, most reports refer to the presence of vascular sclerosis and occlusion within the densely scarred endomyocardial tissues. McKinney[7] mentioned subendothelial deposits of eosinophilic material which decrease the vascular lumen. Connor and associates[3] described an early lesion consisting of medial swelling due to the presence of increased amounts of amorphous polysaccharide material; they also noted a late change represented by vascular sclerosis and partial occlusion of the lumen.

As coronary arterial changes were observed to be frequent in our experience of 12 necropsies in cases of endomyocardial fibrosis, we decided to make a systematic study and description of these changes and to try to interpret their nature and significance.

Material and methods

Complete necropsies were performed in 12 cases of endomyocardial fibrosis. Four of these cases (Cases 1, 2, 3, and 4) appeared in a previous report.[1] Brief general clinicopathological data are presented in Table I. Three of the patients presented with hepatosplenic schistosomiasis; in all the others endomyocardial fibrosis was the

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Table I Clinicopathological data on 12 fatal cases of endomyocardial fibrosis

No	Age (yr)	Sex	Race†	Duration of illness	Heart weight (Gm)	Distribution of endomyocardial fibrosis		Valvular involvement	Intracardiac thrombosis
						RV	LV		
1	27	M	N	2 years	400		*	Mitral	Rt. atrium
2	24	F	N	7 years	380		0	None	None
3	[illegible]	M	N	13 years	280		0	None	Rt atrium
4	28	F	W	2 years	350			None	Rt atrium
5	26	F	M	5 years	670			None	Rt atrium
6	35	F	M	4 years	400			Mitral	None
7	25	M	M	5 month	450	*		Tricuspid	None
8	9	F	W	18 months	200		0	Tricuspid	Rt ventricle
9	[illegible]	[illegible]	M	[illegible] year	400	*	0	Tricuspid	Rt atrium and ventricle
10	62	F	M	3 years	350	*	*	[illegible]	Rt atrium
11	21	F	N	8 months	270		0	None	None
12	14	M	W	7 months	180		0	None	None

Degree of endomyocardial fibrosis arbitrarily graded as mild (*), moderate (**) and marked (***) as to the right (RV) and left (LV) ventricles.
†Abbreviation N = Negro M = Mulatto W = White

main pathological process The hearts presented considerable endomyocardial scarring of one or both inflow tracts of the ventricles and in some instances also of the apex of one or both ventricles (see Table I) The fibrotic areas were contracted the other parts of the hearts showed dilatation All the hearts were fixed in 10 per cent formalin Tissue blocks were taken from several different areas in every case and embedded in paraffin Sections five microns thick were stained by the following methods hematoxylin eosin Mallory's trichrome stain periodic acid Schiff (PAS) Weigert Van Gieson stain for collagen and elastic fibers and Movat's pentachrome stain Paraffin sections of practically every organ of the body were examined with particular attention to the localization of any vascular lesions Chagas disease a common condition in the area was ruled out because no gross or microscopic evidence of that disease was ever present in the cases of endomyocardial fibrosis studied here

Results

Vascular lesions were found mainly within the area of endomyocardial fibrosis which appeared as broad septa penetrating the myocardium from the densely scarred endocardium They were sometimes observed within the uninvolved myocardium and in the adipose tissue of the epicardium (Fig 3) but no comparable changes were found in blood vessels outside the heart Only coronary arteries and arterioles were involved The coronary veins showed no more than edema of the media congestion and occasionally thrombosis For purposes of description the findings will be considered under the following headings

Medial degeneration Medial swelling was frequently seen Sometimes a basophilic amorphous material separates the muscle cells this material was PAS positive and showed the staining characteristics of amorphous polysaccharide material with Movat's pentachrome stain There was swelling of the muscle cell cytoplasm with or without vacuolation These medial changes were particularly severe at the sites of vascular bifurcation where foci of hyaline necrosis were also seen (Fig 1)

Medial focal proliferation Focal areas of muscular hyperplasia were seen in some medium sized arteries usually associated with some degree of medial degeneration or fibrosis

Intimal proliferation This appeared to be associated with deposition of fibrinous material on the endothelial surface of



Fig. 1. *A* through *F*. Several types (probably *evolutionary* stages) of medial degeneration *affecting* the coronary arteries in endomyocardial fibrosis. *A*. Mucoid degeneration. The muscle cells in the media appear dissociated (Hematoxylin and eosin. Original magnification ×150.) *B*. Vacuolation of the muscle cell cytoplasm. (Hematoxylin and eosin. Original magnification ×130.) *C*. Formation *of clefts* in the degenerated media. (Hematoxylin and eosin. Original magnification ×130.) *D*. Medial hypertrophy and sclerosis. (Movat's *pentachrome* stain. Original magnification ×100.) *E*. Medium sized subepicardial coronary artery showing medial fibrosis *affecting* only part of the vessel. (Movat's pentachrome stain. Original magnification ×100.) *F*. Medial degeneration with vacuolation and disappearance of muscle cells and expansion of *mucinous* connective ... is not altered. (Movat's stain. Original magnification ×130.)



Fig 2 *A* through *I* Several stages of the lesions affecting the coronary arteries in endomyocardial fibrosis *A B C* and *D* Small arteries showing intimal fibrin deposit on endothelial cell proliferation intimal fibrosis and the formation of fibrous bands that divide the lumen In *D* the media of the smaller vessel is almost completely replaced by fibrosis (Movat s pentachrome stain Original magnification ×130) *E* and *F* Intimal proliferation and the formation of secondary lumina External to the endothelial cells there is a thin layer of fibrinous material (Movat s pentachrome stain Original magnification ×130) *G H* and *I* Multiluminal vessels The medial coat is almost totally replaced by fibrosis Probably an end stage lesion (Hematoxylin and eosin Original magnification ×130)



Fig. 3. An advanced change represented by medial fibrosis and the formation of new vascular channels within the fibrotic intima. The affected vessel is a medium sized artery within the subepicardial adipose tissue. (Movat's pentachrome stain. Original magnification ×130.)

arteries of various caliber. The fibrinous material formed thin laminar deposits that were often completely covered by endothelium that had proliferated. Fresh fibrinous deposition could be observed side by side with foci of organizing fibrosis of the intima. In some instances fibrin deposition and endothelial proliferation formed spurs that projected into the lumen as 'intimal bridges.' The internal elastic membrane was frequently normal in these vessels, but their media was fibrotic.

Plexiform metamorphosis of vessels. This was the most striking change, but it was present in only 50 per cent of cases. The affected arteries appeared to have several lumina of different sizes lined by swollen endothelial cells. The wall of such vessels was almost totally replaced by fibrous tissue. Focal deposition of fibrin on the endothelial surface and endothelial polyps or projections could still be seen in vessels with advanced plexiform changes (Fig. 2).

Medial sclerosis. Replacement of the medial muscle cells by fibrous tissue was seen in several arteries and arterioles in every case. The fibrous tissue varied from a loose textured basophilic tissue to a densely collagenous one.

Other changes. Several other changes also appeared in relation to the coronary vessel, such as adventitial fibrosis, perivascular edema, congestion, and a slight perivascular lymphocytic accumulation. These changes were considered to be non-specific rather than essentially related to the condition under study.

Comments

The presence of coronary vascular lesions in a disease such as endomyocardial fibrosis is not unexpected. Although the etiology of endomyocardial fibrosis is still obscure, the various theories that have been put forward relate to processes in which vascular changes may be expected. This is true, for example, if we consider endomyocardial fibrosis as a form of rheumatic disease[8] or as a muscle disease[6] or as a hypersensitivity disease of the connective tissue of the heart.[3]

In our cases the lesions in the coronary vasculature were frequent and varied. Although mistakes readily result from trying to base a dynamic interpretation on static morphologic features, we should like to link the several changes observed into a unitary sequence. Because of its frequency we consider medial degeneration to be the fundamental lesion. It is [illegible]ably fol

lowed by fibrosis and by the deposition of fibrin in the intima and the organizing intimal changes The vascular lesions do not seem to be secondary to the endomyocardial fibrosis itself since they also appeared in uninvolved myocardium and in the epicardium They do not appear to represent a primary feature of the disease since there was no correlation between them and the degree of endomyocardium scarring It seems to us to be probable that the changes that result in the intimal and medial fibrosis may be caused by the same still obscure factor or factors that cause the endomyocardial fibrosis The arterial lesions could lead to further myocardial damage and thus be a potentially important element in the pathogenesis of the disease

Medial degeneration in coronary arteries with subsequent sclerosis and calcification has been recognised in man and in experimental animals under several different conditions[9] Usually such medial change are followed by intimal fibrosis but repeated deposition of fibrin and the plexiform metamorphosis of the vessels do not seem to be features of the vascular changes in these cases Medial degeneration of the smaller coronary vessels has also been described in a variety of hereditary musculoskeletal and neuromuscular syndromes[10] As James[11] suggested the possibility that a hereditary medial necrosis of small coronary arteries is responsible for some obscure cardiomyopathies deserves further study

Medial degeneration of the smaller branches of the coronary arteries is an important finding in dogs that have been maintained for long periods on a diet deficient in magnesium[1] A similar lesion has been found in alcoholic cardiopathy[13] It may be significant that hypomagnesemia has been noted in cases of chronic alcoholism and of hepatic cirrhosis[14] Similarly endocardial necrosis that heal with endomyocardial scarring has been found in rats treated with corticoids and sodium salts such necrosis was prevented by the prophylactic administration of magnesium[1] At present unfortunately nothing seems to be known about the magnesium content of the blood of patient with endomyocardial fibrosis

Regardless of their obscure etiology we consider those obstructive coronary arterial lesions that were a prominent histopathological feature of our cases of endomyocardial fibrosis as a pathogenetic element in the progression of this disease

Summary

A series of changes affecting the coronary arteries was found during a postmortem histopathological study of 12 consecutive cases of endomyocardial fibrosis in Brazil These changes seem to represent a spectrum which includes medial degeneration medial sclerosis organizing fibrin deposition on the intimal surface and the formation of plexiform lesions Medium sized and small arteries and arterioles within the fibrotic endomyocardial areas were mainly affected but changes were also seen in other areas of the myocardium and in the epicardium Lesions were not found in the vasculature outside the heart

The lesions in the coronary vasculature resemble morphologically the basic process of fibrosis that affects the endocardium and adjacent myocardium they are more over an important feature of the histopathological picture of the disease and may play a role in the pathogenesis of the accompanying myocardial damage

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Comparison of pulmonary wedge and left atrial pressure in man

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As early as 1906 it was observed that pressure change in the left atrium and pulmonary venous system could be transmitted retrograde to the end arteries of the lungs Pulmonary wedge pressures were first described by Hellems and associates[1] in 1948 The development of left heart catheterization allowed direct measurement of left atrial pressure and provided a means for direct correlation of pulmonary wedge and left atrial pressures On the basis of these studies pulmonary wedge pressures have been used as synonymous with the left atrial pressure in the calculation of mitral valve areas and other hemodynamic indexes The hemodynamic evaluation of patients with acute myocardial infarction has led to the use of pulmonary wedge pressure as an index of left ventricular filling pressure[2,3] This recent use of pulmonary wedge pressure has placed new emphasis on defining the precise correlation of mean pulmonary wedge and mean left atrial pressure Our review of the literature fails to reveal a comparison of pulmonary wedge and left atrial pressures in a large number of patients This study was designed to compare retrospectively mean pulmonary wedge and mean left atrial pressure in a large number of patients with and without heart disease

Methods

The records of 700 patients obtained at cardiac catheterization were analyzed These hemodynamic data were obtained as part of the diagnostic cardiac catheterization at Duke University Medical Center and Durham Veterans Administration Hospital between 1959 and 1972 The patient groups included normals (23) coronary artery disease (54) mitral stenosis (159) mitral insufficiency (50) aortic stenosis (65) aortic insufficiency (39) and patients with more than one valvular lesion (310) Each patient underwent right and left heart catheterization with left atrial pressure measured directly by a transseptal left atrial puncture Pulmonary wedge pressure was repeated multiple times to insure that correct values were obtained Withdrawal of 95 per cent saturated hemoglobin and snapping of the catheter tip on withdrawal of the wedged catheter was used as evidence of a correct wedge position Whenever possible pulmonary wedge pressures and left atrial pressures were recorded simultaneously on equally cali

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Table I. Comparison of mean values, ranges, and standard deviations (mm Hg) for mean pulmonary wedge and mean left atrial pressures for each of the seven patient groups and for all cases

	Group	N	Mean (mm Hg)	Range (mm Hg)	Standard deviation (mm Hg)	Correlation coefficient*
1	Normals	23				
	PW†		7.0	2-15	±0.6	0.92
	LA		6.4	2-12	±0.4	
2	Coronary disease	54				
	PW		9.6	3-31	±0.5	0.91
	LA		9.1	3-25	±0.5	
3	Mitral stenosis	159				
	PW		20.4	7-43	±0.6	0.90
	LA		19.2	6-48	±0.5	
4	Mitral insufficiency	50				
	PW		13.7	4-37	±0.9	0.93
	LA		12.8	3-38	±1.0	
5	Aortic stenosis	65				
	PW		11.0	4-41	±0.8	0.91
	LA		10.8	2-42	±0.9	
6	Aortic insufficiency	39				
	PW		13.5	4-36	±1.1	0.90
	LA		12.9	3-28	±1.0	
7	Mixed valvular disease	310				
	PW		16.0	3-43	±0.4	0.93
	LA		15.9	2-42	±0.4	
8	All cases	700				
	PW		15.4	2-43	±0.3	0.93
	LA		15.0	2-48	±0.3	

*Correlation coefficients are shown for the comparison of mean pulmonary wedge and mean left atrial pressures.
†Abbreviations: PW = pulmonary wedge; LA = left atrial; N = number of patients.

brated gauges. Pressures were measured with Statham P23Db strain gauges and recorded on an Electronics for Medicine DR8 recorder. Mean pressures were obtained by electronic integration of the phasic pressures. Pressures used in this study were measured when the heart rate was below 100 beats per minute. No additional studies were carried out to determine the possible effect of heart rate on the relation between wedge and left atrial pressure. Standard linear regression techniques were used for evaluation of the data.[4]

Results

Table I shows the mean, range, standard deviation, and correlation coefficient for the mean pulmonary wedge and mean left atrial pressure for each of the patient groups. Despite a wide variation in the range of wedge and left atrial pressures, the correlation coefficients for each of the patient groups were found to be nearly identical. Fig. 1 shows a plot of mean pulmonary wedge versus mean left atrial pressure for all patients. Linear regression analysis reveals a correlation coefficient of $r = 0.93$ with a standard error of ±3.0 mm Hg. Note that the degree of scatter increases as the wedge and left atrial pressures rise.

Table II and Fig. 2 reveal a comparison of mean pulmonary wedge and mean left atrial pressure for all of the patients. For this comparison the data were grouped according to a 5 mm Hg increment in mean wedge pressure. The mean difference for each of these groups was computed as the difference between mean left atrial pressure and mean pulmonary wedge pressure. At wedge pressures below 25 mm Hg there

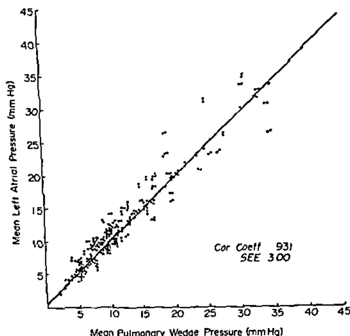


Fig 1 Plot of mean left atrial pre sure versus mean pulmonary wedge pressure (mm Hg) for all patients The regression line was $y = 0.93x + 0.57$ and the correlation coefficient was $r = 0.93$

were no significant differences between mean wedge and mean left atrial pressure In wedge pressure groups 26 to 30 31 to 35 and >35 mm Hg mean left atrial pressure was significantly different from mean wedge pressure ($P < 0.05$) The 95 per cent confidence limits of the prediction of mean left atrial pressure from mean wedge pressure for each of these groups are shown in Fig 2 Note that with a mean wedge pressure of 10 mm Hg or less the error in predicting left atrial pressure is only ±2 mm Hg However the error increases considerably when the mean wedge pressure is higher

Discussion

Hellems and colleagues[1 5] reported experimental evidence that the pressure recorded by a catheter wedged in an end pulmonary artery closely approximated pulmonary capillary pressure Werko and associates[6] Connolly and co workers[7 8] Epps and colleagues[9] and others[10 1] found good correlation between the level of pulmonary wedge and left atrial pressure Other investigators[13 16] in human and animal studies found poor correlation between wedge and left atrial pressure However these early comparisons were performed with left atrial pressures measured in a variety of ways including measurement by way of atrial septal defect [17] by left atrial puncture during open heart surgery[8] measurement by transbronchial approach[9] and measurement by transthoracic approach[6 1 14] Werko and co workers[18] demonstrated that balloon occlusion of the pulmonary artery proximal to the wedged catheter does not alter the pressure recorded at the tip of the catheter demonstrating the left sided origin of the pulmonary wedge pressure Ankeney[19] showed that phasic variations of left atrial pressure waves were transmitted retrograde to the wedged catheter but only mean left atrial pressure was accurately reflected in the wedge pressure tracings Hemodynamic studies on patients with acute myocardial infarction have directed new emphasis on the ability of pulmonary wedge pressure to predict left atrial pressure which is used as an index of left ventricular filling pressure[2 3] Pulmonary wedge pressures (using

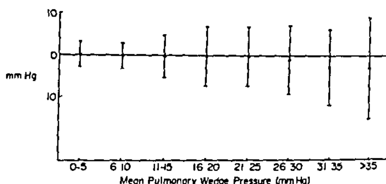


Fig 2 Plot of mean difference in mm Hg of left atrial pressure from mean wedge pressure (mm Hg) in groups of 5 mm Hg of mean wedge pressure Points above and below the zero line signify mean left atrial pressure greater and less than respectively mean pulmonary wedge pressure Brackets surrounding these mean points signify the 95 per cent confidence limits (The 95 per cent confidence limits of the data were determined by multiplying the standard error of the mean by the appropriate T value)[4]

Table II Mean pulmonary wedge pressure vs mean left atrial pressure

Pulmonary wedge pressure group (mm Hg)	N*	Mean difference (mm Hg)	Standard error of the mean (mm Hg)
0 5	39	0	±0
6 10	207	0	±0
11 15	163	0	±0
16 20	111	0	±0
21 25	84	0	±0
26 30	52	−1†	±1
31 35	28	−3†	±1
>35	16	−3†	±1

*N = number of patients in each 5 mm Hg incremental group
†Signifies that the mean difference was statistically significant ($P < 0.05$)

the Swan Ganz catheter) can be monitored at the bedside and if valid can provide vital data on left ventricular filling pressure[20,21] Since left ventricular filling pressure is frequently elevated in acute myocardial infarction, correlation of pulmonary wedge with left atrial pressure must be done over a wide range of pressures

The plot of mean wedge versus mean left atrial pressure (Fig 1) demonstrates little scatter around the regression line until the pressures exceed 10 mm Hg The near identity of the mean differences and the small standard errors between wedge and left atrial pressure suggest that mean pulmonary wedge pressure is a moderately accurate predictor of mean left atrial pressure at these low normal wedge pressures The predictive ability of mean wedge pressure (described by the 95 per cent confidence limits illustrated in Fig 2) is directly related to the level of mean wedge pressure When the wedge pressure is greater than 10 mm Hg the prediction of left atrial pressure can be shown to contain considerable error Ventricular filling pressure and other assessments of myocardial performance and valve areas cannot validly be calculated from the wedge pressure if it exceeds 10 mm Hg The increasing loss of correlation between wedge and mean left atrial pressure at higher pressures may in part be explained by the findings of Caro and associates[22] who demonstrated that high pressures across the pulmonary capillary bed cause a change in the ratio of pulmonary arterial and pulmonary venous compliance promoting asymmetrical trans

mission of pressure waves across the pulmonary vascular bed

The present study was done in a retrospective manner and has all the errors in measurement which are inherent in the day-to-day operation of a diagnostic cardiac catheterization laboratory. Thus it might be argued that meticulous attention to detail in pressure recording might yield a closer correlation. However it is with this level of expertise in pressure measurement that hemodynamic data is collected on a routine basis

Summary

Values of mean pulmonary wedge and mean left atrial pressure were compared in 700 patients including normals and patients with a variety of heart diseases. An over all correlation coefficient r = 0 93 was found between mean wedge and mean left atrial pressure and this correlation was unrelated to the etiology of the heart disease. No significant difference between the average value of wedge and left atrial pressure was found until the wedge pressure exceeded 25 mm Hg. In patients with mean wedge pressures of 10 mm Hg or less left atrial pressure could be predicted with an accuracy of ±2 mm Hg (95 per cent confidence limits). However at higher wedge pressures the prediction of mean left atrial pressure was subject to considerable error. Thus caution should be employed in using mean wedge pressure as an accurate index of mean left atrial pressure unless the wedge pressure is within the low normal range

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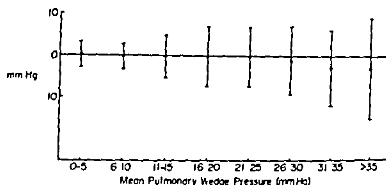


Fig. 2. Plot of mean difference in mm Hg of left atrial pressure from mean wedge pressure (mm Hg) in groups of 5 mm Hg of mean wedge pressure. Points above and below the zero line signify mean left atrial pressures greater and less than, respectively, mean pulmonary wedge pressure. Brackets surrounding the mean points signify the 95 per cent confidence limits. (The 95 per cent confidence limits of the data were determined by multiplying the standard error of the mean by the appropriate T value.)[4]

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The plot of mean wedge versus mean left atrial pressure (Fig. 1) demonstrates little scatter around the regression line until the pressures exceed 10 mm Hg. The near identity of the mean differences and the small standard errors between wedge and left atrial pressure suggest that mean pulmonary wedge pressure is a moderately accurate predictor of mean left atrial pressure at these low normal wedge pressures. The predictive ability of mean wedge pressure (described by the 95 per cent confidence limits illustrated in Fig. 2) is directly related to the level of mean wedge pressure. When the wedge pressure is greater than 10 mm Hg, the prediction of left atrial pressure can be shown to contain considerable error. Ventricular filling pressure and other assessments of myocardial performance and valve areas cannot validly be calculated from the wedge pressure if it exceeds 10 mm Hg. The increasing loss of correlation between wedge and mean left atrial pressure at higher pressures may in part be explained by the findings of Caro and associates[2] who demonstrated that high pressures across the pulmonary capillary bed cause a change in the ratio of pulmonary arterial and pulmonary venous compliance promoting asymmetrical trans

The progression of coronary atherosclerotic disease as assessed by cine-coronary arteriography

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The development of cine-coronary arteriography has enabled the physician to define obstruction of the coronary arterial system and to demonstrate the rate of progression of atherosclerotic coronary artery disease in individual patients. The present study was undertaken to evaluate arteriographic progression of coronary disease in 64 patients, 7 of whom were treated with partial ileal bypass surgery, and to correlate progression with clinical and biochemical parameters.

Groups studied and methods of study

Two groups of subjects were studied. The first group consisted of 8 patients, 7 men and one woman, with hyperlipidemia and severe coronary atherosclerosis documented by coronary arteriography who underwent partial ileal bypass surgery. One subject died early, leaving 6 men and one woman for restudy. Postoperative arteriograms were perfomed in all patients (the mean postoperative interval was 25 months) in order to follow their coronary arterial disease. The second group of 57 patients, 54 men and 3 women, underwent repeat coronary arteriography after an interval of one to 54 months (mean 14 months) to evaluate revascularization procedures or because of progressive symptoms. These two groups are considered separately throughout the study.

Age, height, weight, history of previous myocardial infarction (substantiated by electrocardiographic and/or serum enzyme changes), family history of coronary artery disease, and cigarette consumption were noted. In 63 subjects the presence or absence of glucose intolerance was established by a glucose tolerance or a two hour post-prandial blood sugar test following a standard 100 Gm. oral glucose load. Fasting serum cholesterol levels in all patients and triglyceride levels in 36 patients were determined by standard laboratory methods. Lipoprotein phenotyping was done in 30 patients by the method of Fredrickson and associates.[1] Chest roentgenograms were reviewed to establish the presence or absence of cardiomegaly as determined by the cardiothoracic ratio (greatest transverse diameter of the heart greater than one half the greatest transverse diameter of the chest). A history of myocardial infarction in the interval between coronary

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Table I Clinical and biochemical data for 7 patients in Group I (partial ileal bypass)

Datum	*Value*	
Age	35 ± 10	
Sex (% male)	86%	
Weight (lb)	168 ± 21	
Height (in)	67 ± 2	
Smokers	85%	
Family history of coronary disease	57%	
Carbohydrate intolerance	0	
Serum cholesterol (mg %)		
Preoperative	452 ± 99	(p < 0 001)†
Postoperative	236 ± 42	
Serum triglyceride (mg %) (n = 5)		
Preoperative	211 ± 107	(N S)
Postoperative	112 ± 20	
Past myocardial infarction	27%	
Interim myocardial infarction	27%	
Card omegaly	0	
Left ventricular end-diastolic pressure‡	17 ± 8	
Aortic mean pressure	103 ± 14	
Interval between partial ileal bypass and repeat coronary arteriogram (mo)	25 ± 7	

M ± st dard d iat n
†St d t t t st sed N S. d ote p > 0 05
‡Left tricular nd-diast lic p essure

preoperatively versus 273 ± 95 mg per 100 ml postoperatively) in 5 patients with arteriographic progression ($p < 0.01$) Serum triglyceride levels measured in 5 patients decreased by 47 per cent but this change failed to attain statistical significance (Table I Fig 2) One example of clear-cut progression from this group of subjects is seen in Fig 1 *A* and *B*

Group II (all arteries) Progression was noted in 37 patients (63 per cent) The interval between coronary arteriograms was significantly longer ($p < 0.001$) in patients with arteriographic progression (17 ± 14 months) than in patients without arteriographic progression (9 ± 12 months) There were no significant differences between the two groups in the other parameters measured (Table II) Progression was noted in 57 sites in 50 arteries Seventeen of these sites were in grafted arteries proximal to the saphenocoronary anastomosis No significant progression was seen in a grafted artery distal to the saphenocoronary anastomosis

Group II (excluding revascularized arteries) If vessels subjected to direct revascularization procedures are excluded from the evaluation of progression 19 patients (33 per cent) showed progression involving 40 sites and 33 arteries The difference in the interval between coronary arteriograms in patients with arteriographic progression (23 ± 15 months) versus those without arteriographic progression (8 ± 9 months) is more striking with bypassed arteries excluded ($p < 0.001$) Patients with progressive disease also had significantly higher ($p < 0.01$) mean serum cholesterol levels (Table III) The amount of progression in per cent was divided by the number of months over which the change occurred to derive a rate of progression This rate was then related to the serum cholesterol to determine the correlation coefficient between the two variables but the r value ($p > 0.1$) indicated no significant relation between the two variables Serum triglyceride levels and lipoprotein phenotyping were obtained in only 5 of 19 patients with and 24 of 28 patients without arteriographic progression making statistical comparison of these parameters impractical No significant differences were found between patients with and without arteriographic

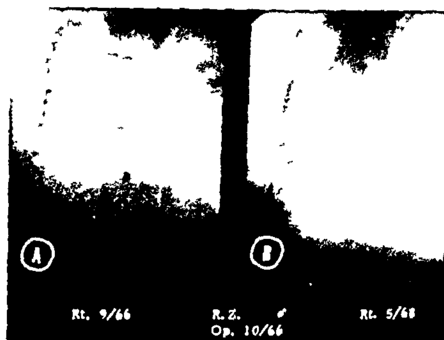


Fig. 1. Right coronary arteriograms of Patient R. Z. showing clear progression. Partial ileal bypass was performed in October 1966.

arteriograms substantiated by electrocardiographic and/or serum enzyme changes, was noted. At cardiac catheterization pressures were recorded in the left ventricle and aorta with special reference to left ventricular end diastolic and aortic mean pressure. Coronary arteriography was performed by the Sones technique[2] in most instances after sublingual administration of 0.4 mg. of nitroglycerin and/or 5 mg. of isosorbide dinitrate and recorded on 35 mm. film with grid pulse control x-ray equipment. Views were taken of the left coronary artery in 60, 45, and 30 degrees of left anterior oblique and 30 degrees of right anterior oblique; the right coronary artery was filmed in 45 degrees of left anterior oblique and 30 degrees of right anterior oblique. Aortocoronary saphenous vein grafts were filmed in 45 degrees of left anterior oblique and 30 degrees of right anterior oblique.

All arteriograms were independently evaluated by both of the authors. When the interpretations were not in agreement the arteriograms were reviewed jointly and a compromise interpretation reached.

Arteriographic criteria for progression were total occlusion of a previously open vessel, an increase of 25 per cent in obstruction of the vessel lumen by a pre-existing lesion, or appearance of a lesion obstructing at least 25 per cent of the lumen of a previously normal vessel.

Forty-one patients underwent direct coronary arterial revascularization procedures to 57 vessels in the interval between coronary arteriograms. Thirty-three patients had 49 saphenous vein grafts, 5 of which were combined with an endarterectomy. One patient had an internal mammary aortocoronary graft. Two patients underwent endarterectomy alone and 5 had an endarterectomy with a patch graft. Twelve patients underwent Vineberg procedures, 3 in conjunction with direct coronary artery surgery.

Statistical analysis was performed using the Student "t" test, the chi square test, or the simple correlation coefficient when appropriate.

Results

Group I (ileal bypass). Five of 7 patients (71 per cent) showed arteriographic progression, one did not have arteriographic progression, and in the other the arteriograms were not technically adequate for evaluation (Fig. 1). Serum cholesterol levels decreased by 48 per cent (452 ± 99 mg. per 100 ml. preoperatively versus 236 ± 42 mg. per 100 ml. postoperatively) in the group as a whole ($p < 0.001$) and 41 per cent (466 ± 117 mg. per 100 ml.

progression in the other parameters measured (see Table III)

Location of lesions The location of obstructive lesions showed a marked predilection for the proximal third of the coronary arteries In Group II as a whole at the time of the initial arteriogram lesions were in proximal locations in 91 per cent for the left anterior descending 81 per cent for the circumflex and 65 per cent for the right coronary artery (Table IV) New or progressive lesions showed this proximal predilection even when bypassed arteries were excluded In the left anterior descending artery 92 per cent of new or progressive lesions involved the proximal third of the vessel This was not as striking in the circumflex artery in which 56 per cent of the new or progressive lesions involved the proximal third or the right coronary artery in which 47 per cent of the lesions were in the proximal third of the vessel (Table V) Only two patients had arteriographic progression of the left main coronary artery One developed 50 per cent obstruction in the vessel which was only slightly involved previously and in the other a 90 per cent obstruction of the left main coronary artery progressed to total occlusion

In an effort to determine whether proximal location or high grade luminal obstruction predisposes to progression the distribution and severity of the lesions at the time of initial arteriography in those whose lesions progressed was compared with those whose lesions remained stable As seen in Table IV the distribution of lesions throughout the vessels was not different for the two groups The mean degree of luminal obstruction by proximally located lesions at the time of initial coronary arteriography was not significantly different in patients with and without arteriographic progression (Table VI)

Surgical results Forty three of the 49 saphenous vein bypass grafts and the single internal mammary bypass graft were patent at restudy for a patency rate of 86 per cent All arteries upon which endarterectomy alone or endarterectomy and patch graft was performed were patent

Of the 50 arteries upon which bypass surgery was performed 13 were completely occluded preoperatively All bypass grafts to these 13 arteries were patent at the

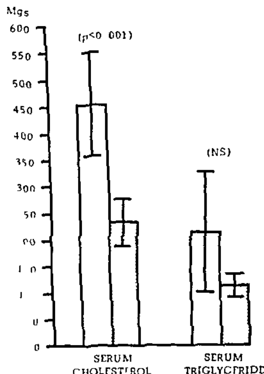


Fig 2 Preoperative (open bars) and postoperative (stippled bars) serum cholesterol and triglyceride levels in Group I patients (partial ileal bypass)

postoperative study Of the remaining 37 arteries 22 appeared to be completely occluded proximal to the saphenocoronary anastomosis postoperatively Patients with and without proximal arterial occlusion did not differ significantly in age serum cholesterol per centage of preoperative occlusion (> 80 per cent both groups) or interval between surgery and postoperative arteriogram Four patients had the unfortunate combination of a nonpatent bypass graft and complete occlusion of the grafted artery

Only 6 of the 34 patients undergoing coronary bypass surgery had evidence of progression in nongrafted vessels The graft patency rate in this group was 67 per cent (6 of 9) as compared to 90 per cent (37 of 41) in the patients without progression in nongrafted vessels ($p < 0.01$) The rate of artery occlusion proximal to the saphenocoronary anastomosis was not significantly different 50 per cent (3 of 6) versus 61 per cent (19 of 31) respectively

Table II. Clinical and biochemical data for patients in Group II (bypassed arteries included)

Datum	*Arteriographic progression (19)*	*No arteriographic progression (38)*
Age	48 ± 9*	49 ± 8
Sex (% male)	94%	95%
Weight (lb.)	172 ± 29	167 ± 21
Height (in.)	67 ± 3	68 ± 3
Smokers	78%	81%
Family history of coronary disease	56%	52%
Carbohydrate intolerance	0	5%
Serum cholesterol (mg. %)	252 ± 48	244 ± 43
Serum triglyceride (mg. %)	170 ± 110 (17)	160 ± 98 (14)
Lipoprotein phenotype	(15)	(14)
II	0	0
III	0	7%
IV	40%	36%
Normal	60%	57%
Past myocardial infarction	42%	33%
Interim myocardial infarction	3%	5%
Cardiomegaly	17%	14%
Left ventricular end diastolic pressure (mm. Hg)†	17 ± 9	19 ± 8
Aortic mean pressure (mm. Hg)	106 ± 22	100 ± 15
Interval between coronary arteriograms (mo.)	17 ± 14	9 ± 12

Number of patients in parentheses.
*Mean ± standard deviation.
†Left ventricular end diastolic pressure.

Table III. Clinical and biochemical data for patients in Group II (bypassed arteries excluded)

Datum	*Arteriographic progression (19)*	*No arteriographic progression (38)*	*p Value**
Age	49 ± 9†	49 ± 8	N.S.
Sex (% male)	95	95%	N.S.
Weight (lb.)	170 ± 17	170 ± 28	N.S.
Height (in.)	69 ± 3	68 ± 2	N.S.
Smokers	82% (17)	86% (36)	N.S.
Family history of coronary disease	63%	54% (37)	N.S.
Carbohydrate intolerance	0	5% (37)	N.S.
Serum cholesterol (mg. %)	276 ± 53	235 ± 47	< 0.01
Serum triglyceride (mg. %)	168 ± 103 (5)	195 ± 102 (26)	
Lipoprotein phenotype	(5)	(24)	
II	0	0	
III	0	4%	
IV	20%	42%	
Normal	80%	54%	
Past myocardial infarction	53%	32%	N.S.
Interim myocardial infarction	5%	3%	N.S.
Cardiomegaly	16%	16%	N.S.
Left ventricular end diastolic pressure (mm. Hg)‡	18 ± 10	18 ± 7	N.S.
Aortic mean pressure (mm. Hg)	105 ± 18	101 ± 16	N.S.
Interval between coronary arteriograms (mo.)	23 ± 15	9 ± 9	< 0.001

Number of patients in parentheses.
*Student t test or chi square used. N.S. denotes $p > 0.05$.
†Mean ± standard deviation.
‡Left ventricular end diastolic pressure.

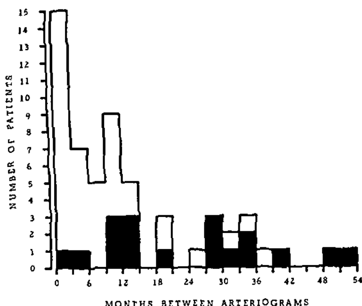


Fig 3 Interval between arteriograms in months and number of patients studied at each interval Shaded squares represent patients with arteriographic progression

Table VI Mean per cent of luminal obstruction by lesions in the proximal third of coronary arteries in Group II patients at the initial arteriogram The group is divided into those patients who showed progression at repeat arteriography and those who did not

Vessel	Arteriographic progression (36)	No arteriographic progression (21)	p Value
Left anterior descending	75 ± 21	80 ± 20	N S
Circumflex	67 ± 20	73 ± 23	N S
Right	71 ± 22	71 ± 25	N S
All vessels	72 ± 21	77 ± 21	N S

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were felt severe enough to require surgical revascularization whereas this had not been the case after the first arteriogram Another patient developed a 50 per cent occlusion of the left anterior descending in 3 months time The significantly higher serum cholesterol levels in patients with arteriographic progression is expected and is in agreement with Bemis and associates[4] who studied 50 patients with repeat cine coronary arteriography (mean interval 23 months) using similar criteria for progression The Bemis group also found elevated serum triglyceride levels to be correlated with progression Ten of 29 patients in our series without arteriographic progression in whom lipoprotein phenotyping was performed were found to be Type IV Had the interval between coronary arteriograms in the patients been longer progression may have been found

It would seem logical that atherosclerotic obstructive coronary arterial disease would progress with time and this is supported by the significantly longer interval between arteriograms in our patients with arteriographic progression than in our patients without arteriographic progression Thus there was progression in 9 of 13 subjects restudied after 2 years and in

Table IV Percentage of lesions involving the proximal third of the coronary arteries at the initial arteriography in Group II patients The group is further divided into patients who showed progression at repeat arteriography and those who did not

Artery	All patients (57)	Arteriographic progression (19)	p Value*	No arteriographic progression (38)
Left anterior descending	91	85	N S	93
Circumflex	81	82	N S	80
Right	65	65	N S	66

Number of patients in parentheses
*Chi square used N. S. denotes p > 0 05

Table V Percentage of new or progressive lesions involving the proximal third of coronary arteries in Group II patients at repeat arteriography

Artery	%
Left anterior descending	92
Circumflex	56
Right	47

Discussion

It is not feasible to compare Groups I and II statistically because of the discrepancies in size and constituency However it is of interest to note that of 6 ileal bypass patients in whom coronary arteriograms were of sufficient quality for comparison there was clear arteriographic progression in 5 patients and in 3 myocardial revascularization was done to relieve progressive angina pectoris despite a very significant reduction in serum cholesterol levels This is in contrast with the experience of Knight and associates[3] who have obtained repeat coronary arteriograms in 18 patients with ileal bypass surgery and found progression in 4 patients Clearly information is needed on the rate of progression of coronary atherosclerosis and whether it is altered by ileal bypass

Myocardial revascularization especially the aortocoronary saphenous bypass procedure has played a prominent role in the therapy of obstructive coronary arterial disease at this institution Consequently few patients have had repeat cinecoronary arteriography without surgical intervention in the interim All arteries including those subjected to surgical revascularization procedures, were initially included in the evaluation of progression (Group II) Bypassed arteries whose proximal portions were not filled by contrast material at arteriography were assumed to be occluded However, because of flow alterations which may occur in arteries subjected to revascularization surgery, it seems reasonable to exclude these arteries from the assessment of progression (Group II excluding revascularized arteries) Occlusion of a bypassed artery at an area of high grade stenosis proximal to the saphenocoronary anastomosis cannot be assumed to be equivalent to atherosclerotic progression in vessels not subjected to bypassed surgery especially when progression was not seen distal to the saphenocoronary anastomosis In addition technical features of the surgical procedure with constriction or clotting at or near the anastomotic site may lead to occlusion Furthermore one must consider the possibility that failure to opacify an area previously shown to be tightly stenotic in the proximal portion of a recently bypassed vessel does not prove that the area is occluded It is difficult to explain why contrast material would flow through a tightly stenotic area when the artery proximal and distal to it are both subjected to equal pressures from the aorta, with the pressure to the distal segment transmitted via a saphenous vein graft

In Group II excluding revascularized arteries clear progression was found in 19 of 57 patients (33 per cent) In one patient the lesions found at the second arteriogram

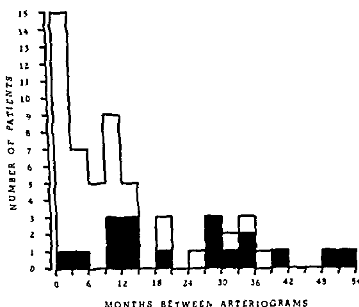


Fig. 3 Interval between arteriograms in months and number of patients studied at each interval. Shaded squares represent patients with arteriographic progression

Table VI Mean per cent of luminal obstruction by lesions in the proximal third of coronary arteries in Group II patients at the initial arteriogram. The group is divided into those patients who showed progression at repeat arteriography and those who did not

Vessel	*Arteriographic progression (36)*	*No arteriographic progression (71)*	*p Value*
Left anterior descending	75 ± 21	80 ± 20	NS
Circumflex	67 ± 20	73 ± 23	NS
Right	71 ± 22	71 ± 25	NS
All vessels	72 ± 21	77 ± 21	NS

Number of patients in parentheses.
Mean ± standard deviation.

were felt severe enough to require surgical revascularization whereas this had not been the case after the first arteriogram. Another patient developed a 50 per cent occlusion of the left anterior descending in 3 months time. The significantly higher serum cholesterol levels in patients with arteriographic progression is expected and is in agreement with Bemis and associates[4] who studied 50 patients with repeat cine coronary arteriography (mean interval 23 months) using similar criteria for progression. The Bemis group also found elevated serum triglyceride levels to be correlated with progression. Ten of 29 patients in our series without arteriographic progression in whom lipoprotein phenotyping was performed were found to be Type IV. Had the interval between coronary arteriograms in the patients been longer progression may have been found.

It would seem logical that atherosclerotic obstructive coronary arterial disease would progress with time and this is supported by the significantly longer interval between arteriograms in our patients with arteriographic progression than in our patients without arteriographic progression. Thus there was progression in 9 of 13 subjects restudied after 2 years and in

only 6 of 36 restudied at one year or less (Fig. 3). We have no explanation for the failure of Bemis and co-workers to find progression related to the time elapsed between arteriograms.

The predilection of atherosclerotic obstructive coronary artery disease for proximal portions of the coronary arterial tree in these patients is in agreement with post-mortem findings.[5-11] As expected, new and progressive lesions as demonstrated here by arteriography shared this proximal predilection. Proximal location and mean degree of luminal obstruction by lesions at initial arteriography were not related to progression.

The 59 per cent rate of occlusion of coronary arteries proximal to the saphenocoronary anastomosis is disturbing, especially when combined with a nonpatent bypass graft. Because of the 86 per cent graft patency rate, this was a relatively uncommon finding in this series. Our data do not suggest any parameters helpful in predicting which arteries will undergo proximal occlusion. They do suggest, however, that patients with progressive disease in vessels not grafted will have lower saphenous vein graft patency rates than those without progressive disease in nongrafted vessels.

Conclusion

Seven of 8 survivors with hyperlipidemia and obstructive coronary arterial disease who underwent ileal bypass surgery had repeat coronary arteriograms. Clear progression of coronary disease was found in 5 patients, despite a significant reduction in serum cholesterol levels. Fifty-seven patients were studied by repeat coronary arteriography to evaluate progressive symptoms or revascularization procedures. Progression was seen in 19 patients (33 per cent). The interval between arteriograms was significantly longer and the serum cholesterol levels significantly higher in patients with progression.

Fifty bypass grafts were performed in 34 patients with a patency rate of 86 per cent. Apparent occlusion of the coronary artery proximal to the saphenocoronary anastomosis was seen in 59 per cent of grafted arteries, and the reliability of this observation is discussed.

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Bifascicular block A clinical and electrophysiologic study

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In the last ten years the electrocardiographic features of bifascicular block have become well defined and their pathological correlations have been described[1-5]

The clinical implications of this abnormality are also better understood Thu it is known that bifascicular block precedes the development of complete heart block in about 50 per cent of patients with complete heart block[6] Since in patients with bifascicular block atrioventricular conduction depends on the anatomic and physiologic integrity of only one fascicle it is reasonable to expect that stress such as anoxemia or drugs which affect atrioventricular conduction may precipitate the development of heart block

The question therefore arises whether patients with bifascicular block who require surgery should have a prophylactic temporary pacemaker inserted prior to operation One also wonders about the safety of administering drugs which influence atrioventricular conduction such as digoxin or quinidine to patients with bifascicular block. The purpose of this paper is to report our experience in 39 patients with bifascicular block who either underwent surgery and/or received antiarrhythmic drugs

The introduction of His bundle recording[7] and atrial pacing[8] provides a clinical method of studying the electrophysiologic mechanism of atrioventricular conduction

Table I Outline of study†*

Underwent surgery	Atrial pacing	Received antiarrhythmic drugs
4 patients—had 38 operations	10—4 of these had surgery	17—3 of these had surgery

*Total number of patients = 39
†Age range = 46 to 90 years.

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Table II Clinical and electrocardiographic features of patients who underwent surgery

Etiology of heart disease	Number	Sex		Syncope	Congestive cardiac failure	Cardiomegaly	Functional disab[illegible]			
		Male	Female				I	II	III	IV
Atherosclerotic heart disease	9	6	3		2	7	5	2	2	
Hypertensive heart disease	3	3	–	–	–	2	2	1	–	
Etiology not known	12*	7	5	–	–	–	12	–	–	
Total	24	16	8	1	2	9	19	3	2	
		24					24			

*Except one patient in whom the etiology may have been traumatic
†New York Heart Association[10]
‡Abbreviations and symbols 1° AVB = first degree AV block LBBB = left bundle branch block RBBB = right bundle branch b[illegible]

These techniques were applied to ten patients in order to determine whether atrial pacing might be predictive of the development of heart block in persons with bifascicular block

Materials and methods

The 39 patients with bifascicular block forming the basis of this report were referred to members of the Cardiology Staff at New York Medical College (Flower and Fifth Avenue Hospital and Metropolitan Hospital) for various reasons during the period of June, 1968 to June, 1972 The charts of these patients were reviewed for a history of syncope evidence of cardiovascular disease, or related conditions such as diabetes mellitus The criteria for bifascicular block were as follows

1 Left anterior hemiblock, that is, left axis deviation more negative than −30 degrees (in the absence of inferior wall myocardial infarction or emphysema) and right bundle branch block—i e , the presence of QRS ≥ 0 12 sec in duration the presence of wide S waves in Lead I and V_6 and wide R waves in Leads aV_R and V_1[9,10]

2 Left posterior hemiblock—i e , right axis deviation of ≥ +95 degrees (provided pulmonary right ventricular hypertrophy, pulmonary emphysema, vertical heart due to slender body build, and extensive lateral wall myocardial infarction could be excluded) and right bundle branch block[9,10]

3 Left bundle branch block (that is a QRS of ≥ 0 12 sec in duration the absence of septal Q waves the presence of notching of the QRS in the left sided precordial leads and ST T waves in the direction opposite to that of the QRS in the left sided leads)[10] and PR interval greater than 0 20 sec Patients undergoing surgery were selected for insertion of prophylactic temporary pacemakers at random provided the patient consented to the procedure

The pacemakers were introduced percutaneously into a femoral vein or by cut down into an antecubital vein under local anesthesia

The tip of the catheter was positioned in the apex of the right ventricle under fluoroscopic control The proximal terminals were connected to a Medtronic demand pacemaker The pacemaker was left in position on demand mode until several days postoperatively

The electrocardiogram (ECG) of all patients was monitored on an oscilloscope throughout surgery and in the recovery room

The presence of any arrhythmia conduction delay or triggering of the pacemaker was recorded Complications such as hypotension and hypoxemia were noted Com

ɔe cf surgery		Type cf anesthesia			Type of block		Electrocardiog am		
jor	Minor	General	Spinal	Regional	LAH & RBBB	LBBB + I A1 Bt	PR interval (msec)	Mean QRS axis (LAH + RBBB)	QRS duration
2	4	2	11	3	9		0 11 to 0 24	−45 to −90	0 12 to 0 16
–	3	1	–	2	3	–	0 16	−30 to −60	0 12
1	8	10	7	2	9	3	0 12 to 0 ?8	−30 to −90	0 12 to 0 16
?3	15	13	18	7	21	3			
38			38		24				

I = left anteri hemiblock

plications from the insertion of the temporary pacemaker were also recorded

His bundle recordings and atrial pacing was performed using the method described by Damato and co workers[8] The A H and H V intervals were measured at each atrial pacing rate and the rate at which heart block developed and the site of the block were noted

Results

Of 39 patients who were studied 24 had various surgical procedures 12 received anti arrhythmic drugs and 10 had atrial pacing (Table I)

There were 27 men and 12 women Their ages ranged from 46 to 90 years with a mean of 68 years Tables II III and IV list their pertinent clinical and electro cardiographic features There were 12 patients with atherosclerotic heart disease as evidenced by myocardial infarction or angina pectoris eight with probable athero sclerotic heart disease (but without a definite history of angina pectoris or myocardial infarction) and six patients with hypertensive cardiovascular disease Eleven patients out of the 39 had no evidence of heart disease other than the conduction abnormality One patient had aortic incompetence due to chronic rheumatic heart disease and one patient presented with bifascicular block following an automobile accident in which he suffered trauma to his chest

Surgical group The 24 patients underwent 38 operations Six patients underwent more than one operation and one patient had six operations during the period under study Of the 38 surgical procedures 23 were classified as major and 15 as minor Laparotomy prostatectomy hysterectomy were classified as major Herniorrhaphy and cataract extraction were classified as minor

Twelve of the operations were performed under general anesthesia 17 under spinal and 7 under regional The general anesthetic agent used was either halothane or nitrous oxide

Of the 38 operations 13 were performed with the prior insertion of a prophylactic pacemaker 9 of these being major and 4 minor operations Fourteen major and 11 minor operations were performed without the prior insertion of a pacemaker (Table V)

There were no complications due to the insertion of the temporary pacemaker in any patient

None of the 24 patients developed either transient or permanent heart block of any degree during surgery or during the first postoperative week Two patients devel

Table IV Clinical and electrocardiographic features of patients who had atrial pacing

Case no	Age	Sex	Etiology of heart disease	Syncope	CHF	Cardiomegaly	Functional classification	ECG—P R interval (sec)	Mean QRS axis	QRS duration (sec)	Had surgery
1	64	F	ASHD	—	—	Yes	II	0 16	−35	0 14	Yes
2	88	M	ASHD	—	—	—	II	0 20	−60	0 16	—
3	62	F	HHD	—	—	Yes	II	0 20	−60	0 12	—
4	70	M	ASHD	Yes	Yes	Yes	III	0 20	−60	0 14	Yes
5	70	F	HHD	—	—	Yes	III	0 20	−60	0 1[illegible]	—
6	72	M	ASHD	—	Yes	Yes	III	0 30	−45	0 16	—
7	74	M	ASHD	—	Yes	Yes	II	0 24	−60	0 12	—
8	65	M	Etiology not known	—	—	—	I	0 24	−60	0 12	Yes
9	46	M	RHD AI	—	Yes	Yes	III	0 24	N	0 12	—
10	70	M	ASHD	—	—	Yes	II	0 24	N	0 18	Yes

*Abbreviations ECG = electrocardiogram N = normal

Table V Number of operations performed with and without prophylactic pacemakers

	No of operations	No of patients
With prophylactic pacemaker	13	11
Without prophylactic pacemaker	25	13
Total	38	24

operative patient with presumed bifascicular block is not warranted Our findings in 24 patients who underwent a total of 38 surgical procedures 23 of which were major are similar One patient had trifascicular block as demonstrated by the His bundle study None of the patients developed transient or permanent heart block during surgery or during the first postoperative week Although the experience of Berg and Kotler[14] and ours involves only 54 patients undergoing a total of 74 surgical procedures, it appears that under the controlled conditions of modern anesthesia and surgery the risk of developing heart block in patients with bifascicular block is small It may be that release of catecholamines during surgery in fact facilitates atrioventricular conduction Isoproterenol has been shown to shorten the A H interval at any given heart rate [8] The need for the routine insertion of a temporary cardiac pacemaker prior to surgery has not been demonstrated It is to be noted however that there were no patients with left posterior hemiblock and right bundle branch block who underwent surgery in either Berg and Kotler s[14] series or ours

Patients with this particular type of bifascicular block may have a different propensity to development of heart block compared to the other types observed[4] There is evidence that in patients with posterior hemiblock the disease process is more extensive and more diffuse [15] Also one of our patients had thoracotomies It is possible that patients with bifascicular block undergoing chest surgery may be more prone to develop heart block due to the action of various cardiovascular reflexes

It is well known that digitalis does not cause impairment of intraventricular conduction However digoxin does prolong conduction in the atrioventricular node[8] and disease of the His Purkinje system is not infrequently associated with delayed conduction through the A V node [15]

In our own cases four of eight patients with bifascicular block also had prolonged AV conduction Quinidine and procaina

Table VI Results of His bundle studies and atrial pacing in ten patients with bifascicular block

Electrocardiogram	Case no	Basal rate			Atrial pacing			Block		
		HR‡	A H (msec)	H V (msec)	Rate	A H (msec)	H V (msec)	Rate	Type	Site
Abnormal LAD + RBBB + normal PR	1	1[illegible]0	160	40	130-165	160-230	40-5[illegible]	165	Wenckebach	Proximal to His
	2	104	90	45	1[illegible]0-150	90-1[illegible]0	45-60	150	None	None
	3	80	90	0	—	—	—	—	—	—
	4	7	125	30	—	—	—	—	—	—
	5†	—	—	—	—	—	—	140	Wenckebach	—
Abnormal LAD + RBB + prolonged PR	6	83	110	150	90-115	100-110	Constant	115	Mobitz II	Distal to His
	7	79	165	80	95-145	165-[illegible]40	Constant	145	Wenckebach	Proximal to His
	8	[illegible]5	1[illegible]0	60	—	—	—	—	—	—
Complete LBBB + prolonged PR	9	[illegible]0	165	40	110-160	165-[illegible]0	Constant	160	Wenckebach	Proximal to His
	10	81	150	60	95-105	150-[illegible]00	Constant	10[illegible]	Wenckebach	Proximal to His

*Atrial pa[illegible] [illegible] induced [illegible] fibrill[illegible]
†B[illegible] [illegible] His study not done because of technical difficulties.
‡HR = heart rate

mide do affect the intraventricular conduction and as shown by Damato and colleagues[16] prolong the H V interval on His bundle recording One might therefore expect that in patients with bifascicular block any of these drugs may further prolong conduction and possibly induce heart block We have data on only 12 patients in none of whom was there an exacerbation of conduction impairment by the use of these drugs in average therapeutic doses The number of patients studied however is too small to make a definitive statement

It is self-evident that it would be useful to have a method for identifying those individuals with bifascicular block who are prone to develop heart block as part of their natural course This would allow the selection of patients for prophylactic pacemakers in order to avoid a possible fatal Stokes Adams attack

His bundle recordings allow more accurate localization of the conduction defect than does the electrocardiogram Thus even in the presence of a normal PR interval A V nodal conduction may be delayed This was found in one of our cases (Case 1) On the other hand a prolonged PR interval in the presence of bundle branch block may be due to disease in the AV node rather than in the contralateral bundle (Case 9)

If there is impairment of conduction in two fascicles only the H V time would be expected to be normal[15] When it is prolonged as was the finding in 5 of our 9 patients (Cases 3 6 7 8 and 10) more diffuse disease involving either the His bundle or the peripheral Purkinje system can be postulated

Atrial pacing has also been used to study atrioventricular conduction It is known that individuals without evidence of any conduction defect develop heart block on atrial pacing at high rates[17] Haft and associates[18] studied His bundle recordings during atrial pacing in 14 patients with bifascicular block and left anterior hemiblock and in four with right bundle branch block and right axis deviation In all these patients the H V interval remained constant and Wenckebach periods developed proximal to the His bundle as in normals Cheng[19] studied ten cases with right bundle branch block and left axis deviation by atrial pacing Nine patients behaved normally as described above and none of these patients developed complete heart block for a follow up period of up to 30 months

One patient developed transient complete heart block during pacing at the rate of 120 beats per minute the block being distal to the His bundle This patient developed Mobitz Type II block and complete heart block one year later

Berkowitz and associates[19] studied six patients with right bundle branch block and left anterior hemiblock One of these patients developed Mobitz Type II block distal to His bundle on atrial pacing and this patient subsequently developed complete heart block In the cases reported here, two out of seven patients studied developed heart block at rates below those found in normals Only a follow up period will show whether these patients will develop heart block and whether this will occur earlier as compared to the other patients in the group

In conclusion, our findings indicate that patients with bifascicular block undergoing surgery do not require the routine insertion of cardiac pacemakers prior to operation The method of His bundle recording during atrial pacing deserves further study as a possible predictive tool in patients with bifascicular block

Summary

The effect of surgery antiarrhythmic drugs and atrial pacing on the atrioventricular conducting system was studied in 39 patients with bifascicular block

Twenty nine patients underwent 38 operations 23 of which were major A temporary cardiac pacemaker was inserted prior to surgery in 13 cases The remaining 25 operations were performed without prophylactic pacemakers In no patient did heart block develop either during surgery or in the first postoperative week

Twelve patients with bifascicular block received digoxin and either quinidine or procainamide in the usual doses In none was exacerbation of the atrioventricular conduction defect observed

Ten patients had His bundle recordings during atrial pacing performed at gradually increasing rates until second degree heart block developed Only two patients developed atrioventricular block at pacing rates below normal one proximal and one distal to the His bundle

The authors wish to thank Dr Jonas Beregov for referring several patients and Drs Joel Dlug and Ralph Schneebaum for helpin in some of procedures

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Twelve patients with bifascicular block received digoxin and either quinidine or procainamide in the usual doses. In none was exacerbation of the atrioventricular conduction defect observed.

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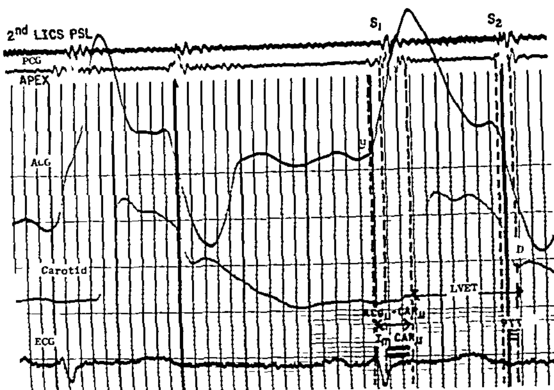


Fig 1 Subject young woman Simultaneous recording from top to bottom of *PCG* = phonocardiogram (second left intercostal space parasternal line) *APEX* = apex phonocardiogram *ACG* = apexcardiogram *Carotid* = external carotid pulse *ECG* = electrocardiogram S_1 and S_2 = First and second heart sounds *D* = dicrotic notch *u* = upstroke of carotid and apexcardiogram *ACG CAR* = isovolumic contraction time from upstroke of ACG to upstroke of carotid pulse I_m-CAR = isovolumic contraction time from high frequency component of first heart sound to upstroke of carotid PTT = pulse transmission time Paper speed = 100 mm per second

splitter to divert it to another AC amplifier with the band pass filter set at 0 1 Hz to 15 Hz The external right carotid arterial pulse tracings were recorded by means of a funnel shaped pickup attached to a Sanborn pulse wave transducer 21051D

Isovolumic contract time (IVCT) was determined by the two methods described by Spodick and Kumar[5]

1 Onset of the first rapid vibrations of the first heart sound to the upstroke of the carotid pulse (I_m CAR) This was also corrected for the pulse transmission time (I_m CAR minus PTT) (see Fig 1)

2 Onset of the apexcardiogram to the upstroke of the carotid pulse (ACG CAR) This was also corrected for pulse transmission time (ACG CAR minus PTT) (see Fig 1) Because indirect recordings cannot be made from the ascending aorta the onset of pressure rise in the carotid artery was utilized instead The time for the transmission of the pulse wave from aorta to the carotid is designated as the pulse transmission time The aortic second sound is coincident with the aortic incisure and therefore the pulse transmission time was measured from the aortic second sound to the carotid incisure This was deducted from the time of onset of the carotid upstroke to indicate beginning of ejection and endpoint of isovolumic contraction time

The left ventricular ejection time (LVET) was obtained from the beginning of the upstroke to the trough of the incisura of the carotid pulse tracing The R R interval was used to determine the heart rate The left ventricular ejection time was corrected by the formula outlined by Weissler

Systolic time intervals in pregnancy and the postpartum period

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Noninvasive techniques have recently been employed to evaluate myocardial function[1-6] The cardiac performance has been assessed after exercise[7] during sustained hand grip after the administration of such agents as amyl nitrate and phenylephrine, and during isorhythmic dissociation[8]

This investigation was designed to assess the effect of a sustained expansion of blood volume on myocardial contractility in normal subjects The isovolumic contraction time (IVCT) and the left ventricular ejection time index (LVETI) were studied in pregnant and postpartum subjects Furthermore the influence of the assumption of the supine and upright positions upon these responses were evaluated

Materials and methods

Sixteen normal women 18 to 36 years of age were studied at the time of maximal expansion of blood volume (at the twenty seventh to thirty third weeks of gestation) Six of the original group were re evaluated six weeks postpartum In addition the ten subjects who did not return for re study were replaced by a comparable age matched group of postpartum women The findings for the original six patients on whom the investigation was repeated in the postpartum period were similar to those obtained for the ten substituted post partum subjects Both sets were therefore combined for the final evaluation of the entire series (See under Results)

All subjects were referred for evaluation from the obstetrical and family planning clinics of a large metropolitan hospital and were entirely free of any medical disability or obstetrical complication

Simultaneous external phonocardiograms electrocardiograms right carotid tracings and apexcardiograms were recorded at rest in the supine position and after assuming the sitting position

The recordings were obtained at a paper speed of 100 mm per second on an eight channel recorder (Sanborn Hewlett Packard 4568 A) Phonocardiograms were obtained at the apex with a 31050 A/B contact sensor (Sanborn Hewlett Packard) using frequency responses 50 to 200 Hz Another microphone was placed at the second left intercostal space at the para sternal line The apexcardiogram was procured from the same contact sensor used to record heart sounds by means of a signal

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positions

LVETI		*SD*	*HR*	
(Mean in msec)			(Beats per min)	
425 1	(16)	13 5	87 2	(16)
412 8	(16)	14 2	94 3	(16)
408 6	(6)	17 0	70 7	(6)
406 1	(10)	18 5	71 9	(10)
407 0	(16)	17 4	71 4	(16)
393 4	(6)	6 4	74 8	(6)
39? 6	(10)	14 2	85 4	(10)
39? 9	(16)	11 6	81 6	(16)

LVETI
0 001
< 0 001
< 0 01
< 0 001

SD = t d d d tio I CAR PTT = iso l mi co tra so l m c co tract n t m from ı troke of pexc d og am t pulse t ssı t me LVETI = left e tr cula jecti

applicable to the pregnant woman and therefore minimized the expected change in isovolumic contraction time upon the assumption of the sitting position However this explanation does not appear to be feasible because the left ventricular ejection time shortened in the pregnant subject in the upright position while in the cardiac patient with increased blood volume the ventricular ejection time remained unchanged

The left ventricular ejection time index (LVETI) in the antepartum subjects both in the supine and upright positions was longer than the comparable LVETI for that position in the postpartum period This again could be attributed to the expanded blood volume and increased stroke volume of pregnancy which operated in both positions In the erect posture however the LVETI shortened significantly and to the same degree in the antepartum as in the postpartum period

In would seem therefore that when the blood volume is at its peak level during the gestation period and the myocardial fibers are lengthened the alteration in systolic time intervals reflects these physiological changes The isovolumic contraction time is abbreviated in response to the greater initial fiber length the left ventricular ejection time is lengthened due to the increase in stroke volume Pregnant women (at least until the terminal weeks of pregnancy) respond to changes in position from the supine to the upright in the expected manner and no evidence of uterine compression upon inferior vena caval flow was noted

The data presented here for the normal pregnant woman could be used in assessing the functional status of cardiac patients in the antepartum and early postpartum periods and for establishing prognostic and therapeutic criteria in the future for these patients

Summary

Systolic time intervals in the supine and upright positions were obtained in 16 antepartum subjects at maximal expansion of blood volume (27 to 33 weeks) and six weeks postpartum Isovolumic contraction time (IVCT) was determined by 2 methods (1) first heart sound to carotid upstroke interval (I_m CAR) and minus pulse transmission time (I_m CAR_u PTT) and by (2) upstroke of apexcardiogram to upstroke of carotid (ACG CAR) and minus pulse transmission time (ACG_u CAR PTT) The IVCT was short in the antepartum supine subject (I_m CAR was 60 5 SD 4 3 msec) and 31 7 msec when corrected for PTT) and became longer in the upright position (63 7 msec [SD 6 1] and 35 6 msec respectively)

In the postpartum state the supine IVCT was significantly longer than in the antepartum state (72 2 msec [SD 9 3] and 42 2 msec when corrected for PTT) (P < 0 001) and became longer in the sitting postpartum subject (85 4 msec [SD 8 8] and 56 8 msec respectively)

The left ventricular ejection time index was 425 1 msec (SD 13 5) in the antepartum supine subject and demonstrated

Table I Systolic time intervals in pregnancy and the postpartum period in supine and sitting

Group	Im CAR ‡ (Mean in msec)		SD	Im CAR PTT (Mean in msec)		ACG CAR (Mean in msec)		SD	ACG CAR PTT (Mean in msec)	
I Antepartum lying	60 5	(16)§	4 3	31 7	(16)	91 0	(9)	7 8	6? 6	(9)
II Antepartum sitting	63 7	(16)	6 1	35 6	(16)	95 0	(6)	5 9	66 5	(9)
III Postpartum lying										
*Group A	70 7	(6)	11 2	40 2	(6)	100 3	(5)	15 9	69 9	(5)
†Group B	73 2	(10)	8 5	43 2	(10)	104 2	(6)	11 7	74 1	(6)
Total series	72 2	(16)	9 3	42 2	(16)	10? 4	(11)	13 1	72 2	(11)
IV Postpartum sitting										
*Group A	85 0	(6)	8 6	56 9	(6)	112 5	(5)	9 6	84 4	(5)
†Group B	85 6	(10)	9 4	56 6	(10)	114 4	(7)	10 6	85 4	(7)
Total series	85 4	(16)	8 8	56 7	(16)	113 6	(12)	9 8	84 9	(1?)

P values	*Im CAR*	*ACG CAR*
Antepartum lying vs sitting	< 0 02	NS (> 0 1)
Postpartum lying vs sitting	< 0 001	< 0 01
Antepartum lying vs postpartum lying	< 0 001	< 0 0?
Antepartum sitting vs postpartum sitting	< 0 001	< 0 001

*Group of original patients that returned postpartum for restudy
†Group of patients substituted for defectors
‡Abbreviations Im CAR = isovolumic contraction time from high frequency component of first heart sound to upstroke of carotid ... *tion time from high frequency component of first heart sound to upstroke of carotid to pulse transmission time* ACG CAR ... to upstroke of carotid ACG CAR PTT = isovolumic contraction time from upstroke of apexcardiogram to upstroke of carotid ... time index HR = heart rate NS = not statistically significant
§Numbers in parentheses indicate number of patients

that we observed Burg and associates[19] obtained similar results when studying subjects in the second trimester of pregnancy These authors however, found that the pre ejection period was longer in the supine position in the third trimester and attributed this to the effect of the enlarged uterus on the venous return This factor assumed greater significance in their patients than in ours One reason for the discrepancies in these observations may have been that our patients systolic time intervals were recorded at the time of maximum increase in blood volume and not in the last weeks of pregnancy The effect of the gravid uterus upon the venous return in this late antepartum period might be greater than the alterations caused by the expanded blood volume

A small but significant lengthening of the isovolumic contraction time was noted when the patients were upright However, after delivery in the postpartum women the isovolumic contraction time was more significantly lengthened on assuming the sitting position This is similar to the effect that Stafford and co workers[20] noted in other normal subjects and has been attributed to the decrease in venous return occasioned by the erect posture In the antepartum women the expanded blood volume may have minimized the effect of the upright position on the IVCT This response is similar to that observed in patients with congestive heart failure The latter subjects demonstrated an unresponsiveness to head up tilt and the systolic time intervals were unchanged in this position [21] They attributed these findings to the antigravitational effects of hypervolumia the elevated tissue pressure and increased venous tone Thi[illegible] [illegible]ht be

Experimental and laboratory reports

Mathematical relationship between automaticity of the sinus node and the AV junction

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Any attempt to define the sequence of events which regulates the normal heart rate must in essence refer to mechanisms which accelerate or slow the sinus node. There are, however, alternate pacemakers and the major substitute pacemaker of the mammalian heart is in or near the AV (atrioventricular) node–His bundle region.[1,2] Despite the current uncertainties as to the exact location of this AV junctional pacemaker, it recently became possible to explore selectively the direct and indirect chronotropic responses of this subsidiary pacemaker in the intact canine heart in situ.[3,4]

For the sake of systematic investigation of normal and abnormal cardiac rhythms it is useful to have quantitative information about stable sinus and A-V junctional rates and from this to establish whether or not there is any mathematical correlation between these two variables. We describe in this paper the data obtained in 50 dogs and their mathematical analysis.

Method

Fifty mongrel dogs weighing 14 to 23 kilograms were anesthetized with intravenous (IV) administration of pentobarbital sodium (30 mg. per kilogram of body weight). Ventilation was maintained through a cuffed endotracheal tube with an intermittent positive pressure Harvard pump supplying room air at 14 to 16 strokes per minute and at a tidal volume of 225 ± 25 ml. Each dog was anticoagulated with sodium heparin (2 mg. per kilogram of body weight) IV. Central aortic and right atrial pressures were measured with catheters positioned by way of the right carotid artery and right external jugular vein and attached to transducers. The chest was opened in the right fourth intercostal space and both the sinus node and the AV node arteries were cannulated with small polyethylene catheters; details of these procedures have been reported.[3,5]

Throughout each experiment a unipolar wick-electrogram from near the sinus node was recorded on a separate single channel electrocardiograph at 25 mm. per second. The same right atrial electrogram was also simultaneously recorded with the two pressures, one or two unipolar electrograms from the right and/or left ventricular surface and a tachogram on a multichannel

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corresponding shortening in the erect position (412 8 msec SD 14 2)

In the postpartum period the LVETI was shorter (407 0 msec [SD 17 4]) and shortest in the upright position (392 9 msec [SD 11 6])

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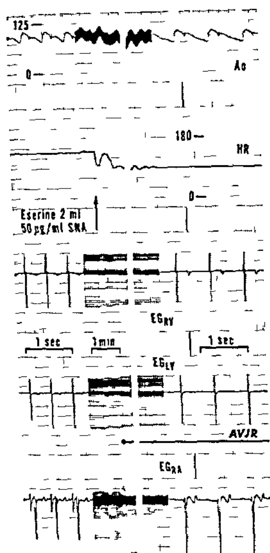


Fig 3 In this polygraph the production of AV junctional rhythm is illustrated following direct perfusion of the sinus node with Eserine Time between the two panels is about 90 seconds and the stable AV junctional rhythm (AVJR) persisted for 25 minutes (other observations from the same dog are illustrated in Figs 1 and 2)

post injection acceleration produced by direct perfusion through the AV node artery with Ringer s solution the rate was identical to the one observed before the injection (Fig 2)

In these experiments an AV junctional rhythm is defined by the three following criteria

1 A regular rhythm not originating in the sinus node during which the *QRS* morphology in the right atrial right ventricular and left ventricular unipolar epicardial electrograms is identical to the same complexes recorded during sinus rhythm (Fig 3)

2 Atrial complexes are within the ventricular complex

3 During AV junctional rhythm the injection of Ringer s solution into the AV node artery produces an immediate AV junctional bradycardia but an injection of Ringer s solution into the sinus node artery has no effect upon heart rate and rhythm (Fig 2) Implicit in the latter criterion is the fact that these two automatic centers respond by immediate slowing during their direct selective perfusion but only when they are functioning as the dominant or active pacemaker

Results

Fig 4 illustrates the typical sequence of injections with the corresponding succession of changes in heart rates and rhythms observed in each experiment At the peak of AV junctional slowing there is inconsistently a temporary slow escape of the previously eserinized sinus node (Fig 5) This sinus escape depends upon (1) the degree of sinus node depression at that particular time and (2) upon the magnitude of AV junctional deceleration Sinus escape can however be produced in any such experiment with these appropriate considerations demonstrating that eserinization of the sinus node does not eliminate potential sinus node activity but simply lowers its level of automaticity below that of the AV junction the sinus node then functioning as a latent rather than an active pacemaker On direct perfusion with Ringer s solution it is only the *driving* pacemaker which decelerates and there are no changes in either heart rate or rhythm following perfusion of the *driven* pacemaker This consistent experimental response permits a simple and accurate distinction between the driving and the driven pacemaker

In the 50 dogs of this study the sinus rate averaged 135 28 ± 25 27 beats per minute (mean ± 1 SD) the range being 84 to 192 The mean AV junctional rate was 87 64 ± 18 95 beats per minute rang

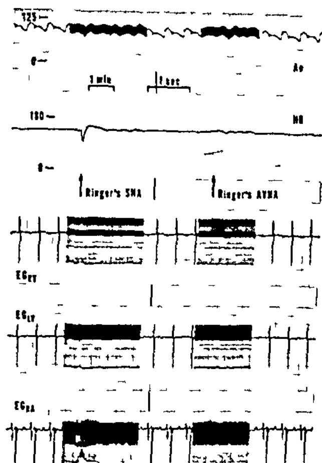


Fig. *1*. This polygraph illustrates the standard recording technique and chronotropic responses to injections of Ringer's solution into the sinus node artery (*SNA*) and AV node artery (*AVNA*) during normal sinus rhythm. Bradycardia during injection and slight post injection tachycardia is characteristic of the response when the nutrient artery perfuses the driving pacemaker as in the first injection above. There is no discernible effect from an injection into a driven or latent pacemaker (second injection here). Recording channels from above down are aortic pressure (*Ao*), tachogram (*HR*), and unipolar electrograms from right ventricular, left ventricular, *and right atrial surfaces. Pressure is scaled in mm* Hg and HR in beats per minute.

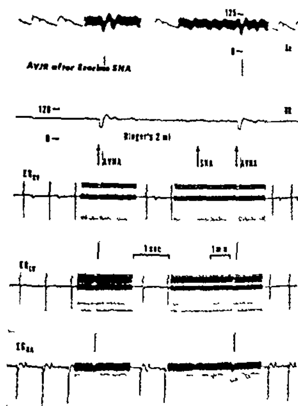


Fig. *2*. When the AV junction is the driving pacemaker, injection into the AV node artery produces bradycardia but injection into the sinus node artery produces no discernible effect.

polygraph at appropriate speed (usually 0.25 or 25 mm per second). The tachogram was derived from successive R waves of either the right or left ventricular electrogram.

After completion of the initial experimental preparation which includes cannulation of both the sinus node and AV node arteries, control sinus rate was recorded before and after sinus node perfusion with Ringer's solution. It has previously been established that the operative procedures per se have no significant electrophysiologic effects.[5,6] The sinus rate was considered stable when after injection bradycardia and post injection acceleration[7] the rate remained identical to the one observed prior to injection (Fig. 1). To assess the accuracy of the response to selective AV junctional perfusion, 2 ml of acetylcholine chloride (0.1 μg per milliliter and 1 μg per milliliter prepared in Ringer's solution) were injected into the AV node artery; experiments were considered satisfactory only if acetylcholine 0.1 μg per milliliter produced an immediate complete AV block for 1 second, or if 1 μg per milliliter similarly blocked AV conduction for at least 2 seconds. To obtain a stable AV junctional rhythm, sinus node activity was gradually depressed by direct perfusion through the sinus node artery with 2 ml of eserine (physostigmine salicylate, 10 to 100 μg per milliliter); validity of this method has been described previously.[4,8] Such escape AV junctional rhythm persists for the duration of cholinesterase paralysis in the sinus node, and in the present experiments averaged 15 ± 5 minutes. AV junctional rate was considered stable when after AV junctional bradycardia and



Fig 4C See legend on opposite page

Table I Analysis of variance for regression of AVJR on sinus rate

Source	d f†	S S	M S	F test
Due to slope	1	399 558 4218	399 558 4218	9 972 33
Additional due to intercept	1	105 09 2	105 0972	2 62 NS
Additional due to lack of linear fit	16	690 3477	43 1467	1 08 NS
Error	32	1 282 1333	40 0667	
Total (uncorrected)	50	401 636 0000		

*Significant at p < 0 001 l
†Abb e ti d f = d g f f eed m S = s m of sq M S = m a sq NS = significant at p = 0 10 l el

that resting AVJR amounts to 66 per cent or two thirds of the resting SR is shown as very close to correct since the calculated value is 64 98 per cent As with most biologic measurements one must allow for potential sources of experimental error such as those inherent in visual reading of electrograms variability of recording paper drive speed and the existing slight inherent deviation from linearity of the tachogram in both high and low frequency range If these and unrecognized other sources of error could be eliminated AVJR would prove to be exactly two thirds of SR although this is speculative The analysis of variance considering the source due to the slope was significant ($p < 0.001$) whereas considering additional sources due to both the intercept and to the lack of linear fit were not significant ($p \approx 0.10$) The model $AVJR = \beta SR$ is therefore adequate to explain the relationship between the two variables AVJR and SR It has further been demonstrated that with a $\hat{\beta}$ estimate of the slope being 0 64979 the t test of the slope is significant at a p < 0 001 level and that the range of the 95 per cent confidence limits for the mean

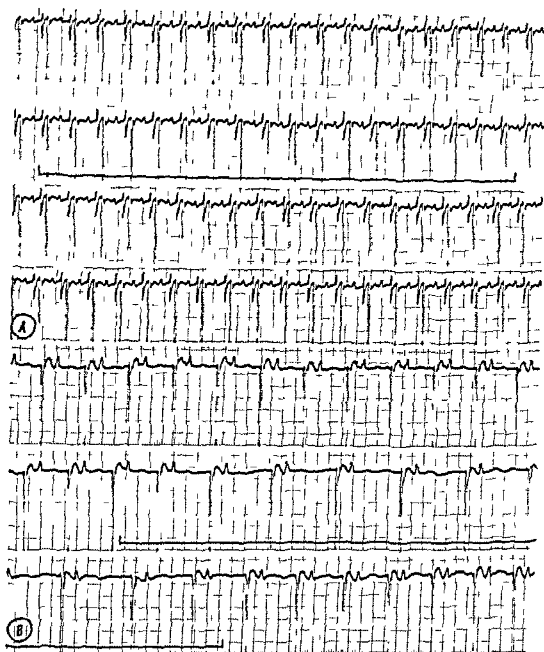


Fig 4 A through C Along with the polygraphs in Figs 1 to 3 the e right atrial electrograms (25 mm /sec paper speed) illustrate the usual sequence of experiments reported Characteristics of the sinus bradycardia during injections into the sinus node artery (SNA) have been published In A there is no discernible effect from injection of 2 ml Ringer s solution into the AV node artery during normal sinus rhythm In B a similar injection during AV junctional rhythm produces slowing but in C an injection into the sinus node artery (after Eserine SNA) has no effect on the AV junctional rhythm These records are from the same dog illustrated in Figs 1 to 3 and are typical of all other records

ing between 48 and 126 Fig 6 represents the cumulative distribution of both the sinus and AV junctional rates As illustrated in Fig 7 by the plot of AV junctional rate (AVJR) versus corresponding sinus rate (SR) each in the same dog the ratio AVJR to SR over the whole range of frequencies is consistently very close to 2 3 The results of statistical treatment[9] of the data are summarized in Tables I and II Under the experimental conditions previously described the rate of a stable AV junctional escape rhythm amounts to about 66 per cent of the resting control sinus rate

Discussion

There is a remarkably consistent correlation ($r = 0.942$ $p < 0.001$) for the linear relationship between the rate of stable sinus rhythm and in the same dog the rate of stable AV junctional escape rhythm A convenient a rem

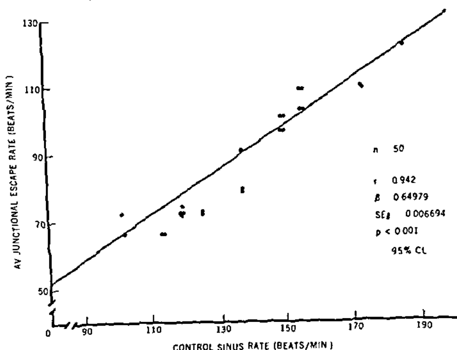


Fig 7 Thi ummary graph illustrates the relationship of escape AV junctional rate to control inus rate each dot representing the two observations in a given dog of the 50 in the series

minute (mean ± 1 SD) the range being 84 to 192 Following selective eserinization of the sinus node (10 or 100 µg per milliliter 2 ml) which progressively slows the sinus node until a stable AV junctional rhythm emerges the mean AV junctional rate was 88 ± 19 beats per minute ranging between 48 and 126 The plot of AV junctional rates (AVJR) versus corre ponding sinus rates (SR) from each dog demonstrates a 2 3 ratio between these two variables On mathematical analysis of these data there is a consistent correlation ($r = 0.942$ $p < 0.001$) for the linear relationship between AVJR and SR with a β estimate of the slope being 0 64979 This value is reasonably close to a useful premise that the resting AV junctional rate amounts to 66 per cent or two thirds of the control sinus rate The model AVJR = $\hat{\beta}$ SR is adequate to explain the relationship between the two variables AVJR and SR

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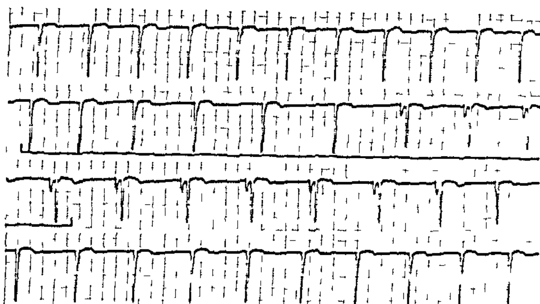


Fig 5 An injection into the AV node artery during AV junctional rhythm (after Exercise SNA) under certain circumstances permit low e cape of the exercised sinus node See text for di cus ion

Table II Final statistics for fit of assumed model AV JR = $\hat{\beta}$SR

Variables	Values
Correlation coefficient (r)	0 94?
Variance of points from fitted line (s^2)	42 3996
Degrees of freedom associated with s^2	49 0
Estimate of slope $\hat{\beta}$	0 64919
Standard error of slope estimate	0 006694
t test of slope	97 07*

*Significant at $p < 0.001$ level

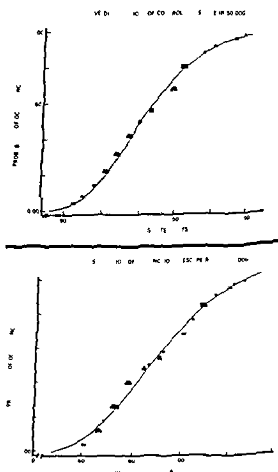


Fig 6 The e two graph illu trate the cumulative distribution of sinu rate and e cape AV junctional rate from the 50 dogs in thi tudy

remains narrow over a wide frequency distribution (Fig 7)

It has been common knowledge since the early use of a Stannius ligature in amphibian hearts and from the work of Meek and Eyster[1,2] on vertebrate hearts that sites of automaticity below the level of the sinus node exhibit decreasing rates of escape activity We are unaware however of any previous systematic analysis of mathematical relations between rates of the sinus node and its major substitute pacemaker observed and documented in vivo The observation in our experiments that the stable AV junctional rate amounts to about 66 per cent of the control sinus rate corresponds closely to the 67 per cent value which Eyster and Meek predicted for the rate of the canine AV node

Summary

Stable sinus and AV junctional rates (each in the same animal) were obtained in 50 open chest dogs anesthetized with pentobarbital After cannulation of both the sinus node and the AV [illegible] arteries the control sinus rate was [illegible]ts p

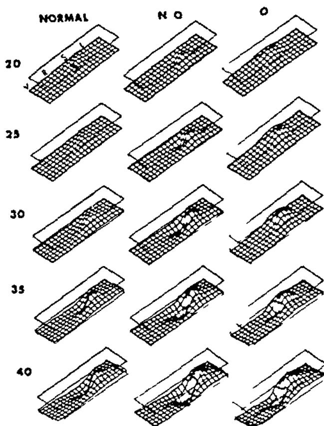


Fig 1 Average isometric projection maps for the group of normal subject the group with nonob tructive cardiomyopathy (N O) and the group with obstructive cardiomyopathy (O) Landmarks applicable to thi and all succeeding figures are indicated in the 20 msec average normal map (upper left) The midsternal line (S) the right m daxillary line (R) the left midaxillary line (L) the vertebral line (V) and the xiphoid process (X) are indicated The plane above the grid represents the 1 mv level The numbers in the left hand column ind cate the millisecond in ventricular depolarization represented by the surface potential grids from each of the three groups The anterior bulge most prominent to the left of the sternum in the normal group represents a combination of left to-right septal activation and early acti ation of the right ventricle [8 9] The mound of pos tivity increases begins to move to the left quite obviously by 30 msec with evidence that right ventricular breakthrough has occurred demonstrated by the dip of negativity seen at 30 msec Thi valley of negativity increases in nagnitude and perimeter through 35 and 40 msec a more of the right and left ventricular epi cardial surface at their septal attachments and later more of the free walls become activated The group with nonobstructi e disea e shows a somewhat earlier dip of negativity which is increased in magnitude and perim ete over the normal but in general follows the normal sequence of activation The obstructive group on the other hand marked by a more prominent pos tive bulge which centers slightly more to the right and repre sent not only septal and normal right ventricular activation but al o the influence of those patients in the group who had right entr cular outflow tract ob truction and associated increase in wall thicknes of the right entr cle and right aspect of the septum The mound increases it positive expression and the delayed right ventricular breakthrough occurs at about 35 msec in contrast with earlier breakthrough noted in the other two groups Electrophys ologic detail is muted by the average maps but the general theme is evident See te t fo further di cussion

had biventricular enlargement and seven had predominantly left ventricular en largement All had an audible S_3 and S_4 at some time during our evaluation except one who had an S_4 only and one who only had significantly elevated left ventricular end-diastolic pressures and decreased dP/dT a sociated with left ventricular enlarge ment but in whom no gallops were heard

All had a history of a regular intake of alcohol on a daily basis for over five years All but one had had frank episode of cardiac insufficiency including not only the reported gallops but râles and an initial significant diuretic response to digitalis No other etiology for their heart failure could be found

The data were obtained by high fre

Comparative surface potential patterns in obstructive and nonobstructive cardiomyopathy

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In this study we will present comparative aspects of two hemodynamically different forms of cardiac muscle disease, obstructive and nonobstructive, both of which cause ventricular enlargement but result in distinctly different expressions of body surface potential. The group of patients with left ventricular outflow obstruction all had nonfamilial idiopathic hypertrophic subaortic stenosis (IHSS). The patients in the remaining group had one of the nonobstructive, nonfamilial types of cardiomyopathy.

Methods

A total of 19 patients with cardiomyopathy were studied by means of body surface potential mapping. In every patient the cardiac diagnosis was verified by means of an extensive cardiovascular history and physical examination, standard electrocardiograms (ECG), posteroanterior and lateral roentgenograms, cardiac survey roentgenograms with barium swallow, and vectorcardiographic (VCG) loops and high-frequency scalar orthogonal leads. In all patients with IHSS and in seven of 13 patients with nonobstructive cardiomyopathy the diagnosis was also supported by cardiac catheterization.

From 142 thoracic sites, selected by means of a cylindrical coordinate marking system, QRS complexes were recorded from 30 normal control male subjects, from six male patients with IHSS, and from 13 male patients with nonobstructive cardiomyopathy. The normal subjects ranged in age from 22 to 29 years. Their normal state was verified by the same diagnostic approaches listed above for the patient groups except cardiac catheterization. In each instance the patients with IHSS had a clearly demonstrated gradient at catheterization from the low left ventricle to the subvalvular chamber and an increase in gradient with pharmacologic stimulation and after ventricular premature beat. The ages of the patients in the nonobstructive group ranged from 27 to [illegible] years with a mean of 40; in the obstructive group the age range was 18 to 55 years with a mean age of 41.3. All patients in the nonobstructive category were also completely free of evidence of alternative or combined etiologic possibilities to explain clear-cut manifestations of ventricular dysfunction. Six

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quency techniques fed into an analog to digital converter and ultimately stored at sampling rates of 1 000 bits per second for final processing by means of a PDP 9 computer These data were then available for display on a storage oscilloscope for hard copy photography in the form of high frequency ECG s VCG scalar leads or loops[1] and isometric projection maps at 5 msec intervals throughout the QRS complex

Maps representing the group average were constructed by taking each individual s digitized data throughout his QRS complex obtained from the 142 sampling sites and averaging with the corresponding instant in the QRS of each member of the group

In Fig 1 the isometric projection grid for demonstrating changes in body surface potential distribution is illustrated Landmarks which apply to all successive grids are seen in the first normal projection map and apply to each successive map the mid ternal line (*S*) the left midaxillary line (*L*) the right midaxillary line (*R*) the paravertebral line (V) and the xiphoid process (X) The plane inscribed above each grid represents the 1 mv level Chest display of positive potential is represented by an outward bulge in the map while negative potential is represented by sinks in the map

Results

Although the technique of map averaging of several individuals tends to mute electrophysiologic detail it does serve the purpose of presenting an over all theme of group differences At 20 msec there is an anterior bulge representing transeptal left to right activation which is also contributed to by early activation of the right ventricular wall near to the attachment of the papillary muscle From about 10 msec on which is not illustrated here there has been some excitation of the right ventricular septal surface[2] The net effect of these wave forms on a body surface potential map then is an outward mound to the right of the sternum with a larger outward mound beginning to move slightly anteriorly and leftward as first the septal attachment and later the free wall of the left ventricle becomes activated At about 30 msec a diffuse elevation occurs whose peak approaches the left midclavicular line at about the fourth intercostal space Breakthrough of the wave of activation to the right ventricular surface (which is represented somewhat earlier in individual maps) probably accounts for the dip of negativity seen by 30 msec which becomes quite prominent by 35 msec By 40 msec a large part of the epicardial surface of the left ventricle has been activated as has much of the right ventricular free wall creating a larger electrical hole in the wave fronts manifested on the surface by the prominent anterior sink[2,3]

At 20 msec in the obstructive group the anterior bulge of positivity is much more prominent and reveals a more significant rightward component reflecting the individuals in this group who had some degree of right ventricular outflow tract obstruction and right ventricular free wall enlargement as well as simply septal hypertrophy[9,10]

By 30 msec in the nonobstructive group the prominent negative sink the surface representation of anteroapical breakthrough on both sides of the septum is a prominent feature while in the obstructive group there is continuation of the prominent outward bulging mound of positivity which has now moved slightly more leftward This mound is increased in amplitude and is prolonged in duration over the normal It is in distinct contrast to the surface sink of negativity which is expected as left ventricular free wall activation proceeds laterally and posteriorly after the electrical front has opened due to epicardial breakthrough of the activation wave in the region of the anterior septum The nonobstructive map in general follows the normal progression with greater prominence of the negative sink which is both deeper and wider This reflects the increased size of the activation front at the time of epicardial breakthrough to the surfaces of the enlarged and more widely separated right and left ventricles

Individual maps of a 41 year old man with nonobstructive cardiomyopathy and a 30 year old man with IHSS make the points much more clearly since averaging has not attenuated detail (Fig 2) At 10 msec a slight bulge of positivity is seen

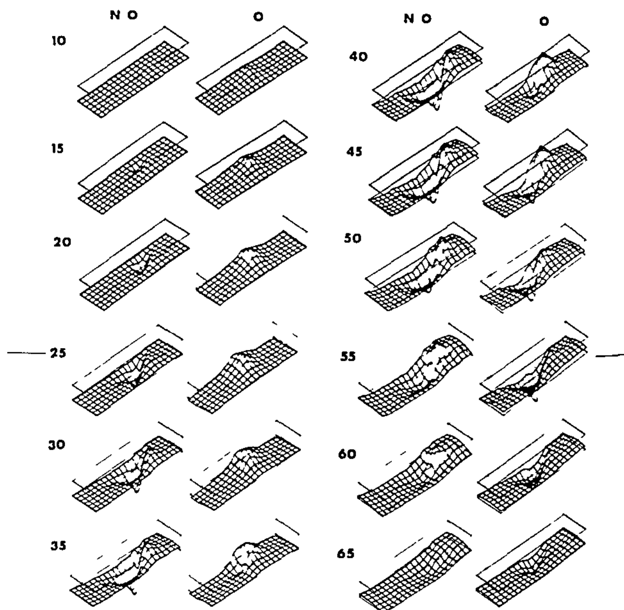


Fig. 2. At intervals of 5 msec individual maps from two patients with hemodynamically distinct forms of cardiomyopathy are illustrated. Under the heading NO are seen the maps of a 41-year-old man with a history of regular alcohol intake on a daily basis for the last 21 years, left ventricular enlargement and failure with episodes of acute pulmonary edema, and the continued evidence of left ventricular dysfunction in the form of S_3 and S_4 gallops, an elevated left ventricular end-diastolic pressure, and decreased indices of contractility. The patient whose maps are seen under the heading O is a 30-year-old man with IHSS with typical physical findings of a rapid rise of the carotid pulse stroke, a prominent bifid arterial pulse, an S_4 gallop, a systolic ejection murmur along the left sternal border without an ejection click which intensifies on Valsalva maneuver and with amyl nitrite and decreases with raising the leg. There were typical findings at cardiac catheterization including a subvalvular chamber with a gradient demonstrated from the low left ventricle. The early rise of positivity is more prominent at 10 msec in the obstructive patient. By 15 msec there is some negative expression as early septal and right free wall breakthrough is expressed in the nonobstructive patient. The mound of positivity in the patient's map with IHSS increases in magnitude and moves to the right by 15 msec. Its further increase in positivity is contrasted with the increasing negativity and rather attenuated positivity in the nonobstructive patient at 20 msec. The positive mound increases and moves leftward through 30 msec with the earliest evidence of right ventricular breakthrough not occurring until 35 msec in the patient with IHSS. Negativity has been manifested in the nonobstructive patient to some extent since 15 msec and reaches its peak by 40 msec with not only prominent magnitude but a very large circumference. Peak negativity in the obstructive patient is not reached until 55 msec, is of lesser magnitude and has a less impressive perimeter. Peak positivity, on the other hand, occurs later in the nonobstructive patient and is more posteriorly oriented.

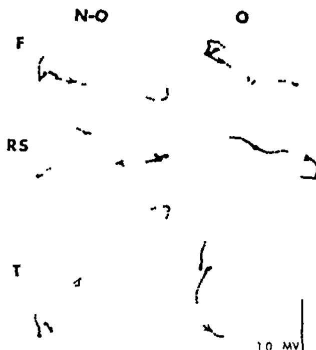


Fig. 3. The left column contains the frontal (*F*), right sagittal (*RS*), and transverse (*T*) loops of the 41 year old man with nonobstructive cardiomyopathy while the right hand column demonstrates the comparable loops in the 30 year old man with IHSS. Note the equatorial but posterior orientation of the loops in the patient with nonobstructive disease which is in distinct contrast to the relatively normal frontal plane axis well below the horizontal demonstrated in the patient with IHSS. The large rounded transverse loop of the patient with IHSS with a significant portion of the loop anterior as well as posterior is in contrast to the posterior figure of 8 in the transverse plane in the case of nonobstructive disease. The dots are at 1 msec. interval and the arrows indicate the direction of the loop at that point. Note the lack of normal early left to right activation in the patient with nonobstructive disease, the early loop slowing noted in all planes in that patient as well as in the patient with obstructive disease. In each instance the arrows are located beyond 24 msec. as determined programmatically from 142 sampling sites from the originally stored digital data. Thus two forms of early activation abnormalities are demonstrated: (1) the failure of normal dominant left to right activation seen in the patient with nonobstructive cardiomyopathy and (2) an abnormal degree of early loop slowing best demonstrated in the patient with IHSS. There was no fal e infarction pattern present in these instances.

in the nonobstructive patient. This bulge is more prominent in the obstructive group and has moved more rightward reflecting the cumulative activation of the septum and the right ventricle near its septal attachment. By 15 msec. in the nonobstructive patient some surface negativity is already apparent as perhaps early right ventricular breakthrough has occurred and has opened the front while, in contrast, in the obstructive patient the dominant positive pattern remains and continues to increase. By 25 msec. the anterior opening in the electrical front is becoming more prominent on the surface at the time the lateral left ventricular muscle mass is being activated in the nonobstructive patient while positivity continues to summate in the obstructive patient. It is not until 35 msec. in the patient with IHSS that a very attenuated sink of negativity appears suggesting that septal and right ventricular breakthrough have occurred. The perimeter of negativity as well as its maximum magnitude is contrasted in the two patients at 40 and 45 msec., while at 50 and 55 msec. the maximum negative dip in the obstructive patient occurs.

In Fig. 3 VCG loops and scalar leads of the same two individuals are illustrated. The equatorial orientation of the VCG loops present in the patient with nonobstructive disease was characteristic of the entire group, with the mean axis hovering close to the transverse plane with very little deviation along the Y axis. In contrast, a much larger percentage of the vector loops in the obstructive group had their mean spatial axes slightly below the horizontal while the transverse loop was almost always large and round with a prominent anterior as well as posterior contribution as seen in the patient illustrated.

Varying degrees of abnormality in the early part of ventricular activation were demonstrated in loops, scalar leads, and body surface maps. The most subtle form of abnormality was frequently seen in the obstructive patients where there was abnormal slowing of the VCG loops in all planes through at least 24 msec. A slightly more apparent abnormality in early activation was seen in over 40 per cent of the nonobstructive patients in whom there was absence of evidence of early left to right septal activation in the scalar leads, VCG loops, or body surface maps. This was manifested as an absent septal Q wave in the X lead or in all of ECG Leads I, aVL, V_5, or V_6, or an attenuated or absent early anterior bulge of positivity in the body surface map. This could also be seen as a lack of the rightward compo

nent of the early direction of the VCG loop The most blatant form of abnormal early activation was seen in one third of our patients with obstructive disease in the form of abnormally prolonged Q waves usually found in the mid and lateral precordial leads but sometimes in other lead sets Abnormality was defined as Q wave duration greater than 0 03 sec though the incidence of abnormality was unchanged when criteria of 0 04 sec or greater were applied[11] Abnormal valleys of negativity accompanied these findings in the body surface map

Discussion

As to the genesis of the faulty left to right activation across the septum neces sary to explain certain of the abnormal findings in the early part of ventricular activation we still lack electrophysiologic detail Septal fibrosis has been offered to explain the lack of normal septal Q but this has been difficult to substantiate morphologically except in about one third of the patients[11]

As to the genesis of the delayed activa tion suggested in the obstructive group and the presence of frankly abnormal Q waves seen in certain obstructive patients the common explanation has been to relate the delayed breakthrough to the right side of the septum to septal hypertrophy Whether this is the case or not is unclear but data obtained by van Dam and associates[12] and Durrer[2] in plunge electrode studies of pa tients with hypertrophic subaortic stenosis strongly suggest another explanation This work suggests almost synchronous activa tion of over half of the thickness of the left ventricular free wall which is in con trast to the expected outward spread of the wave of activation seen in successive layers from endocardium to epicardium causing an electrical gradient with rapid building of the positive expression The epicardial electrode in Durrer s and van Dam s cases continued to see cavitary potential until a much later than expected time in the QRS complex while the plunge electrodes recorded the fact that near to the epicardial surface after simultaneous activation of the underlying subendocardial layers had occurred an activation gradient could be seen to begin then to falter and finally to spread to the epicardium If this general pattern of altered activation occurs with progressively increasing degrees of impair ment in cardiomyopathy and indeed if it obtains in the interventricular septum as well as in the left ventricular free wall it might well explain not only the presence of abnormal Q waves but certain other mani festations of early abnormality of activa tion such as the early slowing of the loop seen in certain patients as well as the false infarction pattern seen in others At this writing however there is no direct electro physiologic data to support the occurrence of actual slowing of conduction or the pres ence of septal activation abnormality

Summary

Extensive noninvasive electrophysiologic studies have been performed on patients with cardiomyopathy Body surface po tential maps in the nonobstructive patients mimicked the normal in the general pro gression of the surface manifestations of activation but demonstrated relatively more prominent patterns of electrical breakthrough in terms of absolute magni tude and in terms of the perimeter of negativity at a given instant in time The pattern of the obstructive group was dis tinctly different being marked by increased magnitude and duration of positivity with an obvious delay in septal right ventricu lar and left ventricular breakthrough con tiguous to the septum with attenuated negativity at the time of those break throughs Maximum negativity also usually occurred 15 to 20 msec later in the patients with IHSS The patients with nonobstruc tive disease characteristically had posteri orly and equatorially oriented VCG loops and often lacked evidence of normal early left to right activation of the interven tricular septum Loops of the patients with obstructive disease were usually oriented below the horizontal and were less pos teriorly oriented Additional abnormalities noted in some patients with obstructive disease included slowing of the loop through at least 24 msec The most extreme form of abnormal sequence of ventricular activa tion was seen in one third of the patients with IHSS in the form of false infarction patterns An electrophysiologic rationale of this latter abnormality has been sug

gested by van Dam and Durrer and is thought by us to represent the best current explanation.

We appreciate the referral of certain patients in this report by Drs. Martin J. Frank and Sankaran Asokan as well as our Cardiology Fellows.

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The effect of heart rate, acetylcholine, and vagal stimulation on antegrade and retrograde His-Purkinje conduction in the intact heart

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Various anatomical studies have demonstrated the presence of cholinergic fibers in the ventricles.[1-7] Acetylcholinesterase activity has also been demonstrated in the canine ventricle.[6] However, the role of these fibers in the electrophysiology of the normal ventricle is not well understood. There have been conflicting reports in the literature. Earlier workers have shown that both vagal stimulation and small doses of acetylcholine have no effect on the transmembrane action potentials of the Purkinje fibers and the ventricular myocardium.[8,9] Later reports have suggested that both vagus and acetylcholine may have an effect on the automaticity, conduction, and morphology of the action potentials of the specialized conduction tissue below the A-V junction.[10-13] The present study was undertaken to evaluate the effect of acetylcholine as well as graded vagal stimulation and heart rate on both antegrade and retrograde His-Purkinje conduction.

Methods

Ten adult mongrel dogs (15 to 35 kilograms) were anesthetized with intravenous pentobarbital sodium (30 mg. per kilogram of body weight). The animals were intubated and artificially ventilated by a Harvard respirator. The heart was exposed through a right lateral thoracotomy at the fourth right intercostal space. As previously described, close bipolar plunge electrodes were used to record electrograms from the region of sinus node (SN), Bachmann's bundle (BB), the right atrial appendage (RAA), the left atrial appendage (LAA), the posterior portion of the left atrium (LAP), and the coronary sinus (CS). Two sets of wires were inserted into the region of the bundle of His.[14,1] One set was used to stimulate and the other pair was used to record the electrical activity of the bundle of His. Additional wires were inserted into the right and left ventricles for pacing. The right cervical vagus was isolated and sectioned. A set of plunge wires

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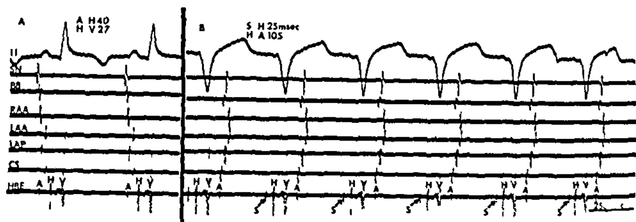


Fig. 1. Panel A shows two sinus beats. In panel B the ventricle was paced at a cycle length of 330 msec. Note the 1:1 retrograde conduction to the atrium. Regrograde His Purkinje conduction (S-H) measured 25 msec. SN = sinus node. BB = Bachmann's bundle. RAA = right atrial appendage. LAA = left atrial appendage. LAP = left atrium posterior. CS = coronary sinus. HBE = His bundle electrogram. A = low atrial septal electrogram. H = His deflection. V = ventricular electrogram. S = stimulus artifact. The above abbreviations are followed in Figs. 2 to 9.

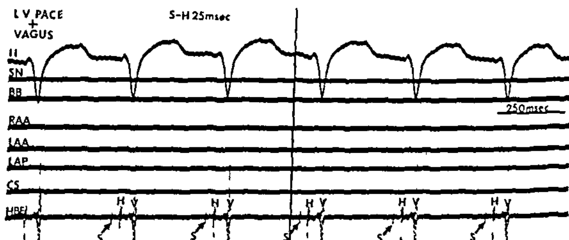


Fig. 2. The ventricle was paced at the same cycle length as in Fig. 1. Note the absence of atrial activity as a result of vagal stimulation. Retrograde His Purkinje conduction time remained the same as in Fig. 1.

was inserted into the distal stump in order to stimulate the vagus nerve. A battery powered pacemaker* which delivered impulses of 2 msec duration at approximately 1½ to 2 times threshold was used to stimulate the bundle of His or ventricles. The vagus nerve was stimulated by a Grass stimulator (Model S 8). The intensity of vagal stimulation was adjusted to produce a graded response varying from slowing of the sinus rate to cardiac arrest with and without atrial fibrillation. This was accomplished by delivering 2 msec impulses at a frequency of 40 impulses per second and at a varying voltage of up to 15 volts. In each study the following procedures were performed. Both the His bundle and the ventricle were paced at varying cycle lengths ranging from 400 to 240 msec. The tracings were repeated with vagal stimulation and acetylcholine injection. Acetylcholine was injected into the femoral vein at a rate of 0.05 mg per kilogram per minute and this resulted in slowing of the sinus rate, increase in the A-V nodal conduction time, followed by atrial asystole. All records were taken on a multichannel oscilloscopic photographic recorder at a paper speed of 200 mm per second.*

The following intervals were measured and expressed in milliseconds (msec.). The A-H interval was measured from the onset

*Medtronic Inc. (Model 5837), Minneapolis, Minn.

*Electronics for Medicine, White Plains, N.Y.

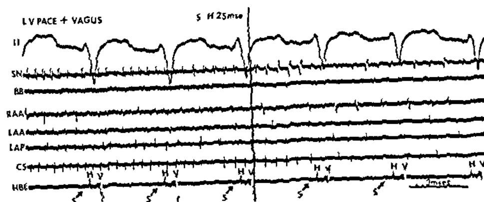


Fig 3 Vagal stimulation resulted in atrial fibrillation and complete heart block Ventricular pacing at the same cycle length as in Figs 1 and 2 demonstrated similar retrograde His-Purkinje conduction time (*S H* = 25 msec)

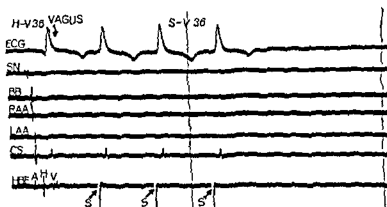


Fig 4 The lack of effect of vagal stimulation on antegrade His-Purkinje conduction (see text)

of the low atrial depolarization (A) to the onset of the His deflection (H) The S A interval during bundle of His pacing was measured from the stimulus artifact to the low atrial septal electrogram of the retro grade atrial impulse (A) The H A interval during ventricular pacing was measured from the retrograde His deflection to the low atrial septal electrogram of the retro grade atrial impulse Both the S A and H A intervals were considered to represent retrograde conduction time through the A V node

Antegrade His Purkinje conduction time was measured from the His deflection to the onset of ventricular activation during sinus rhythm (H V) or from the stimulus artifact to the onset of ventricular activa tion during bundle of His stimulation (S V) During ventricular pacing the in terval from the onset of the stimulus arti fact to the onset of the retrograde His deflection was used as a measure of retro grade His Purkinje conduction time (S H) Validation of the retrograde His deflection was obtained by demonstrating that the H A interval during ventricular pacing was the same as the S A interval during His pacing

Results

Vagal stimulation In all ten dogs the effects of vagal stimulation on antegrade and retrograde His Purkinje conduction were evaluated during bundle of His and ventricular pacing at cycle lengths (CL) varying from 400 to 240 msec At all CL of pacing vagal stimulation had no effect on either antegrade or retrograde conduction as compared to control Representative examples are presented in Figs 1 to 3 (same experiment)

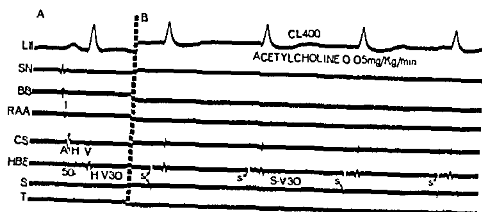


Fig 5 The effect of acetylcholine on antegrade His-Purkinje conduction time

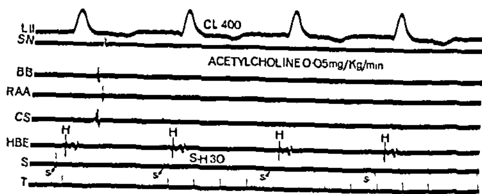


Fig 6 Acetylcholine in doses sufficient to produce cardiac arrest had no effect on retrograde His Purkinje conduction

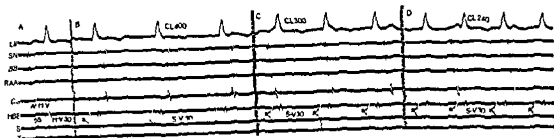
Panel *A* of Fig 1 illustrates two sinus beats in which the A H and H V intervals are 40 and 27 msec respectively In panel *B* the left ventricle was stimulated at a CL of 330 msec One to one retrograde conduction to the atria occurred Retrograde His Purkinje conduction time (the interval between the stimulus artifact and the retrogradely activated His bundle deflection or S H interval) measured 25 msec Retrograde A V nodal conduction time as indicated by the H A interval was 105 msec

In Fig 2 vagal stimulation sufficient to cause cardiac arrest was applied The left ventricle was stimulated at the same CL as in Fig 1 Note the absence of atrial activity Retrograde His Purkinje conduction time (S H interval) remained at 25 msec

Vagal stimulation first resulted in cardiac arrest followed by atrial fibrillation with complete A V block (Fig 3) The left ventricle was then stimulated at a cycle length of 330 msec Retrograde His Purkinje conduction time remains constant at 25 msec

The effects of vagal stimulation on antegrade His Purkinje conduction are illustrated in Fig 4 The first beat is the last of a series of sinus beats The interval from the antegrade His deflection to the onset of the ventricular depolarization (H V interval) measured 36 msec Vagal stimulation resulted in cardiac arrest as evidenced by the absence of spontaneous atrial activity Immediately after vagal stimulation was applied the His bundle was stimulated for three beats at a CL of 315 msec The S V interval was the same as the H V interval during sinus rhythm Following cessation of His bundle pacing the continued effects of vagal stimulation are noted

Effect of acetylcholine The effects of acetylcholine infusion on antegrade and retrograde His Purkinje conduction were also evaluated during bundle of His and ventricular pacing at cycle lengths varying from 400 to 240 msec At all cycle lengths of pacing acetylcholine had no effect on either antegrade or retrograde His Purkinje conduction as compared to control Representative examples are presented in Figs 5 and 6 (same experiment)



F 7 Antegrade His-Purkinje conduction is not influenced by pacing the bundle of His at cycle lengths varying from 400 to 240 msec (see text)

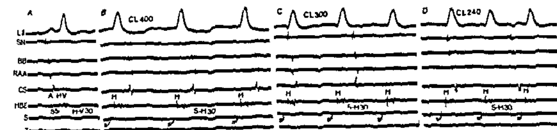


Fig 8 Panel A shows single sinus beat with A H and H V intervals of 55 and 30 msec respectively During ventricular pacing (panel B to D) at decreasing cycle lengths the S H interval remains constant at 30 msec

Fig 5 shows the effect of acetylcholine on antegrade His Purkinje conduction time A sinus beat with an H V interval of 30 msec is shown in panel A In panel B cardiac arrest occurred following injection of acetylcholine and bundle of His pacing at a cycle length of 400 msec resulted in an S V interval which was the same as the normal H V interval of the sinus beat (30 msec)

In Fig 6 the right ventricle was paced at a cycle length of 400 msec The first beat shows retrograde activation of the atria Following this atrial arrest occurred as a result of acetylcholine injection Retrograde His Purkinje conduction time (S H 30 msec) was the same before and after acetylcholine

Effect of heart rate In all animals both the His bundle and the ventricle were paced at cycle lengths varying from 400 to 240 msec to evaluate the influence of the heart rate on the antegrade and the retrograde *His Purkinje* conduction In addition retrograde His Purkinje conduction was also evaluated at cycle lengths as short as 160 msec

Panel *A* of Fig 7 demonstrates that normal antegrade His Purkinje conduction time (H V) measured 30 msec Panels *B* to *D* show that antegrade His Purkinje conduction time (S V 30 msec) remained constant during bundle of His pacing at cycle lengths varying from 400 to 240 msec Fig 8 demonstrates that ventricular pacing between cycle lengths of 400 to 240 msec had no effect on retrograde His Purkinje conduction time

However when the CL of ventricular pacing was decreased to 200 msec or less retrograde His Purkinje conduction delay and block were noted as shown in Fig 9 Panel *A* shows a control sinus beat with an H V interval of 35 msec In panel *B* the ventricle was paced at a cycle length of 200 msec There was a 1 1 retrograde conduction to the bundle of His with a constant S H interval In panel *C* the cycle length of pacing was reduced to 190 msec This resulted in 2 1 retrograde block to the bundle of His alternating with Wenckebach type of block In panel *D* a fixed 4 1 retrograde block to the bundle of His occurred at a paced ventricular cycle length of 160 msec

Discussion

The present study demonstrated that both vagal stimulation and acetylcholine have *no effect on* antegrade or retrograde

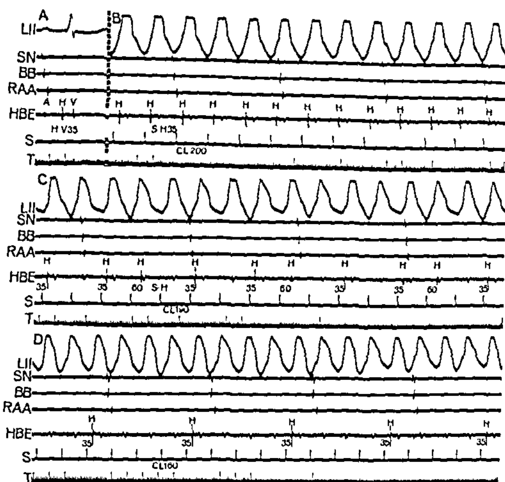


Fig. 9. Panel A shows a sinus beat with antegrade His Purkinje conduction time of 35 msec. Panels B to D show the effect of ventricular pacing at cycle lengths varying from 200 to 160 msec on retrograde His Purkinje conduction (see text).

His Purkinje conduction time. This is in marked contrast to their profound effects on A-V nodal conduction.[16-20] Our results support the findings of Alanis and associates[21] who demonstrated that antegrade His Purkinje conduction (H-V interval) was unaffected during vagal induced cardiac slowing. The present findings are also consistent with the observations that vagal stimulation and acetylcholine have no effect on the transmembrane action potentials of Purkinje and ventricular muscle fibers.[8,9] Recently Bailey and associates[11] showed that superfusion with acetylcholine enhanced conduction in spontaneously firing Purkinje fibers. They demonstrated that with the *infusion* of acetylcholine the cells became less automatic, take-off potential increased, rate of rise of phase 0 was enhanced, and conduction became more rapid. However, this enhancement of conduction with acetylcholine was shown in fibers with spontaneous phase 4 depolarization.

The results of the present study are also in agreement with the clinical observation that the electrocardiogram during effective carotid sinus massage, apart from slowing the atrial rate and producing some A-V nodal delay, fails to show any change in the duration and morphology of the QRS complex. The lack of QRS changes implies that antegrade His Purkinje conduction is unaffected. A remote possibility is that His Purkinje conduction is uniformly affected and consequently a change in the QRS complex would not be evident. This appears unlikely in view of the evidence of the present study.

In both the experimental animal and man progressive increases in the rate of atrial stimulation result in a progressive prolongation of A-V nodal conduction time.[9,17,18] Similarly, a progressive increase in retrograde A-V nodal conduction time occurs as the rate of His bundle or ventricular stimulation is increased.[1] In this respect the His Purkinje system (HPS) dif

fers from the A V node Both antegrade and retrograde His Purkinje conduction times are not affected by increasing rates of atrial or ventricular stimulation This lack of effect is due to the influence of heart rate on the refractory periods of the HPS and the myocardium [22, 23] With increasing rates the refractory periods of both the HPS and ventricular myocardium are progressively shortened and as a result His Purkinje conduction remains unaffected but this response is true only up to certain heart rates With very fast rates (cycle length 190 to 160 msec) various degrees of retrograde block to the HPS occurred The site of block may be at the Purkinje muscle junction or at any site along the HPS wherever the site of maximum refractoriness occurs

The mechanism of this type of block between the myocardium and the HPS can be explained as follows At very fast rates instead of progressive shortening of the refractory period of both the HPS and the myocardium a dissociation of the refractoriness of these tissues may occur While the refractory period of the myocardium shortens the refractory period of the HPS may remain the same This would result in various types of block and may set up a situation for re entry

The observation of retrograde block into the HPS at very fast ventricular stimulation may have some clinical significance Since dissociation of the refractoriness between the myocardium and the HPS occurs at very fast rates one might speculate that the same phenomenon may occur with a very closely coupled ventricular premature beat If this premature beat is sufficiently delayed in the HPS then some areas of the ventricular myocardium might be recovered and be ready to be depolarized again Thus an intraventricular re entry could occur which might give another explanation for some forms of ventricular tachycardia and ventricular fibrillation initiated by a closely coupled ventricular premature beat

Summary

In ten dogs the effects of acetylcholine graded vagal stimulation and heart rate on both antegrade and retrograde His Purkinje conduction were evaluated His bundle pacing was used to obtain the antegrade His Purkinje conduction time and pacing the ventricle and recording the retrograde His bundle electrogram gave the retrograde His Purkinje conduction time Acetylcholine and vagal stimulation sufficient to produce cardiac arrest had no effect on antegrade and retrograde His Purkinje conduction Similarly pacing at cycle lengths varying from 400 to 200 msec had no effect on antegrade or retrograde conduction time However when the cycle length of ventricular pacing was decreased to less than 200 msec various degrees of retrograde His Purkinje conduction delay and block developed

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Drug failure in reducing pressor effect of isometric handgrip stress test in hypertension

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Lind and associates[1] and Donald and associates[2] showed that sustained muscular contractions produced a marked increase of mean arterial pressure, heart rate, and cardiac output.

Recently it was revealed that isometric handgrip contractions (IHC's) of patients with coronary artery disease,[3] with high left ventricle end-diastolic pressure,[4] and with ischemic heart disease[5] produced higher increase of blood pressure than normals. This simple technique of handgripping has been investigated as a tool to detect abnormal left ventricle function.[6,7] The mechanism of action of this cardiovascular response to sustained exercises *is not fully understood.* The present investigation was performed in order to study: (1) the effect of IHC on the blood pressure in groups of normotensive subjects and untreated hypertensive patients and (2) the effect of a number of antihypertensive drugs with different mode of action on the blood pressure changes produced by IHC in hypertensive patients.

Methods and subjects

In the first experiments two groups of subjects were used. In one group were 12 normotensive volunteers: five were male and seven were female; three were Caucasian and nine were Negro; their ages ranged from 20 to 82 years (mean = 50.42, S.E.M. ±4.01). Of these volunteers, eight were normotensive patients of the Eye Clinic who were not taking medications and four were healthy employees of the Washington Hospital Center. In the other group were 14 hypertensive patients (persons whose diastolic pressure had been more than 90 mm. Hg on more than one occasion and without obvious renal or endocrine disorder as its cause). The ages of these patients ranged from 21 to 77 years (mean = 51.93, S.E.M. ± 4.97); five were male and nine were female; three were Caucasian and 11 were Negro. Electrocardiograms (ECG) were made on all patients before the beginning of the experiment. Hypertensive patients with systolic pressure of more than 200 mm. Hg, diastolic pressure more than 130 mm. Hg, with previous myocardial infarction, angina pectoris, stroke, accelerated hypertension, or heart failure were excluded from the study. All patients were off medications for at least one month before entering the study. There was no significant difference

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Table I. ECG's of untreated hypertensive patients before entering the study

ECG	No. of patients
Within normal limits	9
Left ventricular hypertrophy	3
Left anterior superior hemiblock	1
Occasional premature ventricular contractions	1

between the ages of hypertensive and normotensive subjects, race and sex distributions of both groups were comparable.

Technique of handgripping. Before the onset of the experiment, each subject was instructed in the technique of IHC test. After ten minutes in the sitting position, blood pressure of the left arm was measured by a research nurse and then the subject pulled the Handdynamometer* with the right hand and the load of 25 per cent of the maximal voluntary contractions (MVC) was maintained for three minutes. Blood pressure was recorded at rest and at the end of three minutes of IHC.

In subsequent experiments the effects of chronic administration of several antihypertensive drugs on the pressure response to IHC were measured. The 14 hypertensive patients were treated in a cross-over trial according to a randomized block design.[8] The following drugs were used: hydrochlorthiazide (25 mg. three times a day), guanethidine (50 mg. a day), reserpine (0.25 mg. twice a day), and hydralazine (25 mg. three times a day). All drugs were given orally and each period of treatment lasted four weeks. All patients were ambulatory with a normal diet and their blood pressure was recorded every two weeks at the same time of the day and in the same environments. Two blood pressure measurements were made as a baseline prior to drug therapy. At each clinic visit the blood pressure response to IHC was evaluated. The average of two blood pressure measurements at two-week intervals before and after treatments with each drug was computed and analyzed statistically.

*Smedley Handdynamometer from Stoelting Company, Chicago, Ill.

Table II. Mean blood pressure at rest of untreated hypertensive patients (first visit) and normotensive subjects

	Mean blood pressure at rest (mm. Hg)	
	Systolic	Diastolic
Hypertensive	153.00	100.85
S.E.M.	±5.89	±3.80
Normotensive	132.67	86.00
S.E.M.	±3.00	±2.17
t	3.08	3.40
P	<0.01	<0.01

Statistical evaluation was performed in two ways: for the first set of experiments where two groups were compared, the t test was utilized. In the second set of experiments the effect of several drugs on IHC was measured by analysis of variance.

Results

Table I lists the ECG's of 14 untreated hypertensive patients before entering the study. The mean systolic and diastolic pressure at rest in hypertensive and normotensive subjects is described in Table II. There was a highly significant difference of blood pressure at rest between hypertensive and normotensive subjects. The percentage of blood pressure increase during IHC was calculated from the initial resting pressure. It is shown in Table III that the percentile increase of systolic and diastolic pressure after three minutes of exercises was significantly higher in the hypertensive group, while the mean load of IHC differed nonsignificantly. Three hypertensive patients who had electrocardiographic evidence of left ventricular hypertrophy did not have higher response to IHC than the other eleven hypertensives.

In subsequent experiments we have shown that hydrochlorthiazide, guanethidine, reserpine, and hydralazine at fixed dosage during four weeks reduced the systolic and diastolic pressure of hyperten-

Table III Mean percentage of blood pressure increase after three minutes of IHC and the mean load of IHC in untreated hypertensive patients (first visit) and normotensive subjects

	Mean blood pressure increase after 3 min of IHC (% of initial resting pressure)		Mean load of IHC (kg)
	Systolic	Diastolic	
Hypertensive	18 79	21 35	8 4
SEM	±4 22	±4 51	±0 59
Normotensive	6 91	8 61	8 00
SEM	±1 87	±2 00	±0 62
t	4 08	2 58	0 47
P	<0 01	<0 05	NS

NS = t g fi t

Table IV Effect of drug therapy on resting blood pressure of hypertensive patients (average of two visits)

	Mean resting blood pressure (mm Hg)	
	Systolic	Diastolic
Before drug therapy	154 71	101 93
After drug therapy		
Hydrochlorothiazide	130 85	88 86
Guanethidine	143 92	92 85
Reserpine	138 85	88 57
Hydralazine	135 85	91 15
F	3 32	3 40
P	<0 05	<0 05

sive patients significantly (Table IV) The antihypertensive effect of one drug differed nonsignificantly from the others One patient could not tolerate guanethidine and he was considered a drug failure one other patient was a drug failure on hydralazine

Table V shows the effect of drug therapy on blood pressure increase to IHC in hypertensive patients and the mean load of IHC There were no significant differences between the means of percentage increase of systolic and diastolic pressure after three minutes of IHC in patients prior to therapy and after treatments with hydrochlorthiazide guanethidine reserpine and hydralazine During these experiments the mean load of contraction (25 per cent MVC) was not significantly different

Discussion

Many investigators have shown that psychological stress[9] as well as cold pressor tests[10] produced an abnormally large rise of blood pressure in hypertensive patients Both the cold water stress and psychological stress tests depend upon altered vascular reactivity to the sensory inflow resulting from such stresses The IHC on the other hand adds the dimension of work (intense muscular contraction)

In our test subjects hypertensive patients had a larger rise of blood pressure (systolic and diastolic) during IHC than did normotensive persons This greater pressure response to IHC stress was true not only in absolute terms but also as percentage of the initial resting pressure We agree with other investigators[11] that comparison of percentile changes of blood pressure is more desirable because it computes the initial stage of arteriolar reactivity In our study most of the hypertensive patients had a normal ECG but in the absence of hemodynamic determinations we could not exclude any abnormal left ventricular function which would contribute to the presence of higher pressure response to IHC

In the cross over trial in hypertensive

Table V. Effect of drug therapy on the blood pressure increase after three minutes of IHC and the mean load during IHC in hypertensive patients (average of two visits)

	Mean blood pressure increase after 3 min. of IHC (% of initial resting pressure)		Mean load of IHC (Kg.)
	Systolic	Diastolic	
Before drug therapy	16.54	16.33	8.56
After drug therapy			
Hydrochlorthiazide	13.55	14.60	7.86
Guanethidine	12.73	14.52	7.96
Reserpine	13.60	14.01	8.06
Hydralazine	12.63	10.84	7.80
F	0.63	0.58	0.34
P	N.S.	N.S.	N.S.

patients we have shown that hydrochlorthiazide, guanethidine, reserpine, and hydralazine reduced the resting blood pressure significantly but did not affect the pressure response to IHC. Shapiro[12] showed that therapeutic doses of chlorthiazide and reserpine failed to reduce the blood pressure response to cold pressor and psychological tests. He suggested that hyperreactivity of blood pressure response to several types of stimuli in hypertensives is a constitutional character of these patients. Using several antihypertensive drugs with different mechanism of action, our findings give support to this hypothesis.

It is common clinical practice to measure blood pressure at rest, preferably after several minutes in the supine position in a quiet room. There is already voluminous literature on the effect of varying stresses in the life of hypertensive patients which may well have an effect on their life expectancy and incidence of complications. The present study suggests the use of IHC as a standard test for investigation, follow-up, and management of hypertension.

The failure to reduce pressure response to IHC and other stress, including psychological tests, by presently available antihypertensive drugs, has important therapeutic implications. It underlines the need for a general review and advice on the life pattern of hypertensive patients as an adjunct to the therapeutic regimen. The Veterans Administration Cooperative Study Group on Antihypertensive Agents[13] recently reported the beneficial effect of therapy on the morbidity and mortality rates of even moderate to moderately severe hypertensive patients, but could not ascertain the benefit with regard to the progression of coronary heart disease. Our present findings point to a limitation of drugs in the total management of hypertension and suggest further studies on pharmacologic means to deal with the hypertensive effect of stress.

Summary

A pilot study is reported on the isometric handgrip contraction (IHC) test comparing its effects on the blood pressure of normotensive and untreated hypertensive persons and evaluating the effect of antihypertensive drugs on this test. IHC caused a greater percentile increase of blood pressure in untreated hypertensive patients, and this hyperreactivity of systolic and diastolic pressure to IHC stress is not affected by therapeutic doses of hydrochlorthiazide, guanethidine, reserpine, and hydralazine.

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The role of beta adrenoceptors in the coronary and systemic hemodynamic responses to emotional stress in conscious dogs

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Studies in man and in conscious dogs have shown that marked changes occur in the cardiovascular system during emotional stress [1-4] The response is characterized by increases in heart rate arterial blood pressure and cardiac output and by a reduction in peripheral vascular resistance The elegant studies by Rayford and associates[3] also demonstrated marked changes in coronary hemodynamics in conscious dogs during emotional stress There were increases in mean and stroke coronary blood flow and a marked reduction in coronary vascular resistance

As the sympathetic nervous system plays an important role in mediating the cardiovascular responses to emotional stress the development of drugs which specifically block beta adrenoceptors has provided a new and useful tool for analysis of the contribution of activity of these receptors to the hemodynamic reactions to stress Propranolol has been shown to reduce the increases in heart rate and cardiac output and the decrease in peripheral vascular resistance during emotional stress in man [2] Oxprenolol almost completely abolished an emotional tachycardia in ski jumpers.[5] Similar results have been obtained by Pitt and associates[4,6,7] in conscious dogs undergoing stress The changes in heart rate arterial pressure cardiac output, and peripheral vascular resistance were completely blocked by propranolol In the same experiments propranolol did not alter the coronary hemodynamic response to stress These results give further evidence that the systemic hemodynamic response to emotional stress is largely controlled by the sympathetic nervous system but do not clarify the role of beta adrenoceptors in mediating the changes in the coronary circulation occurring during emotional stress in conscious dogs

As beta adrenoceptors blocking drugs have been reported to possess different degree of action on beta receptors located in different tissues and additional properties—e g local anesthetic or quinidine like activity and intrinsic sympathomimetic activity [8,9] we decided to compare the effects of four beta adrenoceptor blocking

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drugs propranolol sotalol (MJ 1999) practolol (ICI 50172) and alprenolol (H 56/28) on the systemic and coronary hemodynamic responses to emotional stress in conscious dogs

Methods

Healthy mongrel dogs weighing 14 to 18 kilograms were used in these experiments The surgical procedures and postoperative care of the animals were similar to those previously described[10] and will only be described briefly Anesthesia was induced by the intravenous injection of thiopentone 30 mg per kilogram of body weight and maintained by artificial respiration with oxygen to which halothane (2 per cent to 3 per cent) was added when required The chest was opened through the fourth left intercostal space and the heart was exposed Electromagnetic flow transducer (Biotronex Laboratories) were implanted around the left circumflex coronary artery and the ascending aorta A pneumatic cuff was applied to the left coronary artery proximal to the flowprobe Inflation of the cuff to occlude the artery was used to determine zero flow postoperatively A polyethylene catheter filled with a solution of 0 9 per cent NaCl was inserted through a carotid artery until its tip was shown by radioscopy to be in the aortic arch

Observations were not made until 15 days after insertion of the flow probes and aortic catheter when all dogs were in good health Phasic aortic and coronary flow tracings were obtained by means of an electromagnetic flowmeter (Biotronex Laboratories) Phasic and mean aortic pressure were measured by a Statham P 23 Db transducer connected to the aortic catheter Postoperatively the electrocardiogram was obtained by parasternal electrodes attached to the skin with adhesive tape The electrocardiogram aortic pressure and phasic and mean aortic and coronary flow were recorded on an 8 channel Beckman Type R Dynograph Stroke volume and stroke coronary flow were measured by planimetrical integration of the areas beneath the respective phasic flow patterns of at least 3 consecutive cardiac cycles

The following parameters were calculated mean systemic resistance (mean aortic pressure in mm Hg/cardiac output in ml per minute) stroke resistance (mean arterial pressure in mm Hg/mean coronary flow in ml late diastolic coronary resistance was also calculated using the procedure of Rayford and colleagues[2] Left ventricular work/time in kg m per minute was calculated as a product of cardiac output (liters per minute) and mean aortic pressure (mm Hg × 13 6)

Emotional stress was induced in all dogs by an auditory stimulus In order to standardize the stimulus a starting pistol the detonations of which were approximately of the same intensity on each occasion was used The responses to excitement were determined four times in each dog on each day on two occasions 30 minutes apart during a control period and 5 minutes after the intravenous injection of 0 2 and 1 0 mg per kilogram of body weight of each drug The results obtained from all the parameters were submitted to an analysis of variance which was carried out on the differences between the data recorded at zero time and those observed 2 6 and 10 seconds after each pistol shot A two way cross-classification was used difference between groups (Control stress 1 Control stress 2 and 5 minutes after 0 2 and 1 0 mg per kilogram of body weight of each drug) and difference between dogs

The following drugs were used propranolol (Inderal Imperial Chemical Industries Ltd) sotalol (MJ 1999 Mead Johnson Ltd) practolol (ICI 50172 Eraldine Imperial Chemical Industries Ltd) and alprenolol (H 56/28 Aptin A B Hassle) All drugs were dissolved in a sterile solution of 0 9 per cent NaCl the doses are expressed in terms of the salt Dilutions of isoprenaline were made from the commercial stock solution *

Results

Response to emotional stress The systemic and coronary hemodynamic responses to an auditory stimulus in a conscious dog are shown in Fig 1 After firing the gun the dog although trained to lie on its left side became restless and shivered An increase in the rate of respiration was observed Heart rate increased to a maximum of 250

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I act lol nd prop nolol d A. B Hassle for alp lol

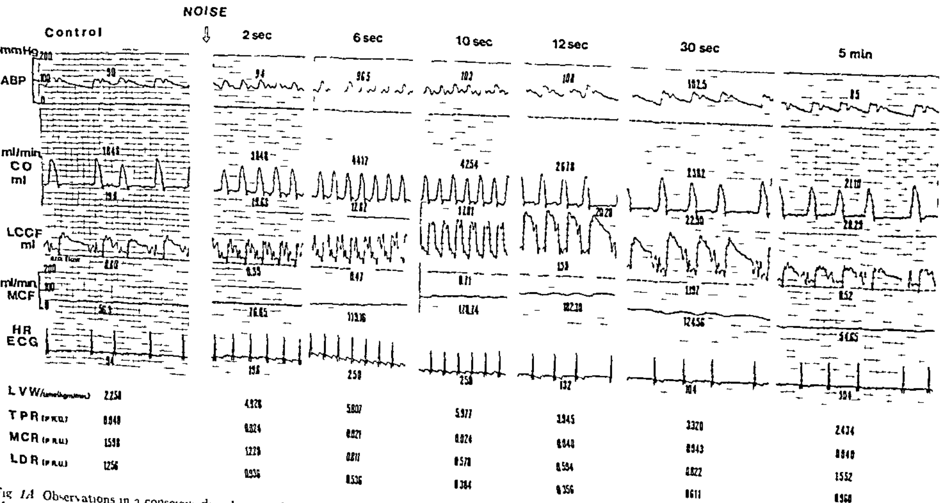


Fig 1A Observations in a conscious dog showing the effect of alprenolol on the responses to *stress*. Records obtained before and at intervals after the firing of a pistol are aortic pressure (*ABP*), phasic aortic flow (*CO*), phasic and mean left circumflex coronary flow (*LCCF*, *MCF*) and the electrocardiogram. The figures on the records from above downwards are mean arterial pressure, cardiac output, stroke volume, stroke coronary flow, mean coronary flow and heart rate. *LVW* = left ventricular work. TPR = total peripheral resistance. MCR = mean coronary artery resistance. LDR = late diastolic coronary resistance. These records were obtained before the administration of alprenolol

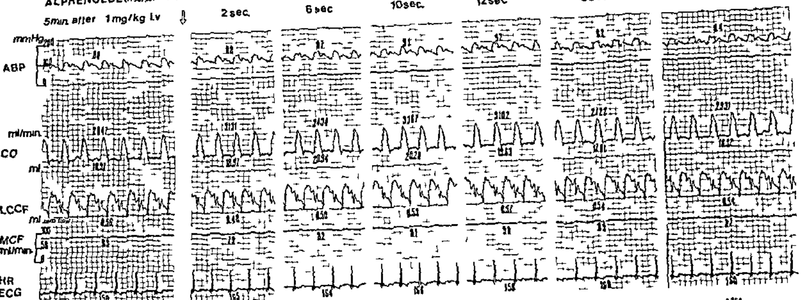


Fig. 1B Record obtained for a conscious dog after the administration of alprenolol 1 mg per kilogram of body weight by intravenous injection. For explanation see legend to Fig. 1 1

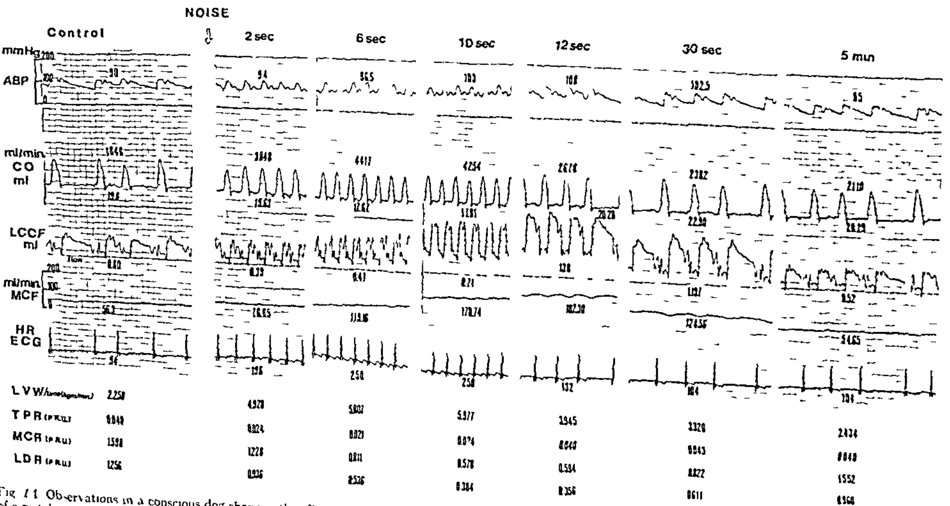


Fig. 11 Observations in a conscious dog showing the effect of alprenolol on the response to stress. Records obtained before and at intervals after the firing of a pistol are aortic pressure (*ABP*), phasic aortic flow (*CO*), phasic and mean left circumflex coronary flow (*LCCF*, *MCF*) and the electrocardiogram. The figures on the records from above downwards are mean arterial pressure, cardiac output, stroke volume, stroke coronary flow, mean coronary flow and heart rate. *LVW* = left ventricular work. TPR = total peripheral resistance. MCR = mean coronary artery resistance. LDR = late diastolic coronary resistance. These records were obtained before the administration of alprenolol.

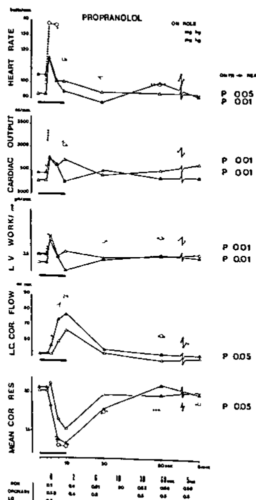


Fig 3 Effect of the intravenous injection of propranolol 0 2 and 1 0 mg per kilogram of body weight on the re ponses to stress in conscious dogs Averaged results from 3 dogs at selected intervals before and after the application of stress on 4 occa sion Re ponses O—O mean of 2 sets of results be fo e propranolol Δ — Δ re ult after propranolol 0 2 mg per k logram of body weight ▲ — ▲ results after propranolol 1 0 mg per kilogram of body we ght Legend and determination of values for p were sim lar to those in Fig 2 with Δ p and ▲ p refer ing to effects of p opranolol 0 2 and 1 0 mg pe kilogram of body we ght respectively

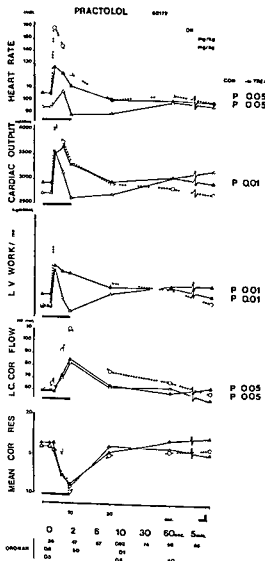


Fig 4 Effect of the intravenous injection of practolol 0 2 (Δ — Δ) and 1 0 (▲ — ▲) mg per kilogram of body weight on the responses to stress in con scious dogs averaged results from 3 dogs Pre sentation of results and legends as in Figs 2 and 3

in mean and late diastolic coronary resist ance and the increase in mean coronary flow produced by stress were significantly reduced after propranolol 0 2 mg per kilo gram of body weight but they were un altered after propranolol 1 mg per kilogram of body weight

Effects of practolol The averaged results from the three dogs which received practo lol 0 2 and 1 0 mg per kilogram of body weight are given in Fig 4 Practolol 0 2 mg per kilogram of body weight signifi cantly reduced the increases in heart rate cardiac output left ventricular work and left coronary flow produced by stress No further changes were produced by practo lol 1 0 mg per kilogram of body weight The increase in stroke coronary flow in re sponse to stress before practolol was not

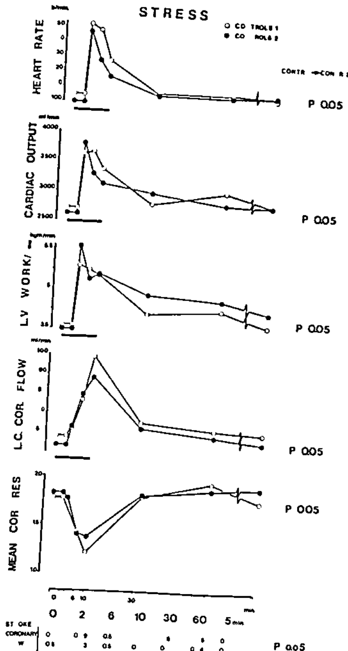


Fig 2 Responses to two stressful stimuli applied 30 minutes apart in 4 conscious dogs The averaged results from the 4 dogs for heart rate cardiac output left ventricular work left circumflex coronary flow stroke coronary flow and mean coronary resistance obtained at intervals after application of the stimulus are shown Responses O — O first stimulus ● — ● second stimulus Values for p were determined for the differences between the two runs using the accumulated results obtained during the period indicated by the solid bar (0 2 6 and 10 seconds)

beats per minute within 10 seconds and then declined rapidly Mean aortic pressure increased during the same time from 90 to 108 mm Hg Although stroke volume decreased, cardiac output was raised from 1,846 to 4 417 ml per minute due to the cardiac acceleration As arterial pressure and cardiac output were increased at the same time, the calculated external work of the left ventricle increased from 2 26 to 5 97 kg m per minute while total peripheral resistance decreased from 0 048 to 0 021 P R U

Coronary flow was greatly increased in response to the stimulus and reached its highest value at 12 seconds which was 2 to 6 seconds after the peak values for heart rate and cardiac output Systolic and diastolic coronary flow decreased 2 seconds after the stimulus and then increased so that stroke coronary flow increased from 0 60 to 1 58 ml at 12 seconds The concomitant increase in heart rate contributed to an increase in mean coronary flow from 56 to 182 ml per minute when the mean coronary resistance fell from 1 59 to 0 59 P R U Systolic diastolic and late diastolic coronary resistances were all reduced The percentage of cardiac output entering the left circumflex coronary artery at rest was 3 05 it rose to a maximum of 6 81 twelve seconds after firing the gun Five minutes after application of the stimulus all values except arterial pressure and cardiac output had returned to normal

Similar changes were obtained in all dogs in response to the first stimulus on each day of observation A second stimulus was applied about 30 minutes after the first when all values had returned to normal There was no significant difference between the responses to these two stimuli (Fig 2)

Effects of propranolol Observations were made in three dogs in which the responses to stress were elicited before (2 occasions) and after the intravenous injection of propranolol 0 2 and 1 0 mg per kilogram of body weight The averaged results from the three dogs are given in Fig 3 The administration of propranolol (0 2 mg per kilogram of body weight) reduced heart rate cardiac output left ventricular work and mean coronary flow stroke volume and stroke coronary flow were unaltered and mean and late diastolic resistance were increased Propranolol 0 2 mg per kilogram of body weight significantly reduced the increases in heart rate cardiac output and left ventricular work which occurred in response to stress No further change in the systemic responses occurred after propranolol 1 mg per kilogram of body weight The reduction

and practolol produced small and not significant changes in resting systemic hemodynamics and in coronary blood flow and vascular resistance. This confirms earlier observations by Pitt and colleagues[12] and by Bergamaschi and co-workers,[10] which showed that in conscious dogs propranolol does not increase coronary vascular resistance. Alprenolol, which had already been shown to possess intrinsic sympathetic activity,[10] significantly increased heart rate, cardiac output, and left ventricular work but decreased systemic resistances.

Although the outward signs of emotional stress were still present after administration of all four drugs, the hemodynamic responses to stress were significantly altered. All drugs significantly reduced the increases in heart rate, cardiac output, aortic pressure, and left ventricular work. These reductions were produced by the smaller dose (0.2 mg. per kilogram of body weight) of propranolol, practolol, and alprenolol, but only by the largest dose (1 mg. per kilogram of body weight) of sotalol.

It has been reported[13] that the hemodynamic response to stress in the conscious dog is similar to that recorded during sympathetic stimulation. Subsequent experiments[4,6] showed that the sympathetic nervous system is predominantly involved in the response to stress. The present results confirm that the systemic hemodynamic changes elicited by stress are largely mediated by beta adrenoceptors as they were significantly altered by all four drugs. Similar results[3] were obtained in pilots training in a flight simulator; the increases in arterial pressure, heart rate, and cardiac output induced by this stressful situation were markedly inhibited by propranolol.

Although the hemodynamic responses to stress were significantly reduced after the administration of propranolol, 1 mg. per kilogram of body weight, changes still occurred in all parameters. The mechanism of these increases in heart rate, cardiac output, and left ventricular work is not clear. They are unlikely to result from incomplete blockade of beta adrenoceptors, as several studies[14,15] have indicated that propranolol, 1 mg. per kilogram of body weight, produces a high degree of blockade of these receptors. The increase in heart

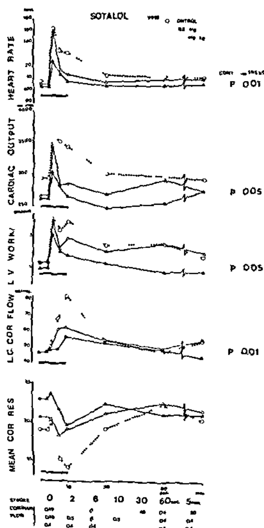


Fig. 6. Effect of the intravenous injection of sotalol, 0.2 (△ — △) and 1.0 (▲ — ▲) mg. per kilogram of body weight on the responses to stress in conscious dogs, averaged results from 3 dogs. Presentation of results and legends as in Figs. 2 and 3.

rate in response to stress after propranolol may result from a reduction in vagal inhibitory activity to the heart; such a mechanism contributes to the increase in heart rate produced by exercise after the administration of propranolol.[16] However, it is not known whether the mechanism of the changes in cardiac function after propranolol in response to exercise and to emotional stress have a common origin. If they have, the increases in cardiac function produced by stress after beta blockade may result from both withdrawal of activity of the

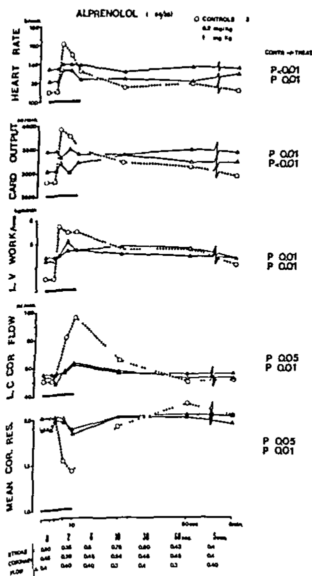


Fig 5 Effect of the intravenous injection of alprenolol 0 2 (Δ — Δ) and 1 0 (▲ — ▲) mg per kilogram of body weight on the responses to stress in conscious dogs averaged results from 3 dogs Presentation of results and legends as in Fig 2 and 3

altered after both doses of the drug Similar reductions in mean and late diastolic resistance occurred in response to emotional stress before and after the two doses of practolol

Effects of alprenolol The results of an experiment showing the response to stress before and after alprenolol 1 mg per kilogram of body weight, are shown in Fig 1 The responses before the drug have been described above The administration of alprenolol increased heart rate cardiac output, and left ventricular work Although the increase in heart rate was accompanied by a decrease in stroke coronary flow mean flow through the left circumflex coronary artery was increased Systemic and coronary resistance were slightly decreased The hemodynamic responses to stress after the administration of alprenolol 1 mg per kilogram of body weight, were markedly altered The increases in heart rate cardiac output left ventricular work, and coronary flow were greatly reduced The reduction in systemic and coronary resistance were also inhibited The averaged results from three dogs which received alprenolol 0 2 and 1 mg per kilogram of body weight, are given in Fig 5 The increases in heart rate cardiac output, and left ventricular work produced by stress were significantly reduced after alprenolol 0 2 mg per kilogram of body weight and almost completely blocked after 1 mg per kilogram of body weight The changes in coronary flow and resistance were reduced to the same extent

Effects of sotalol The averaged results from the three dogs which were given sotalol, 0 2 and 1 mg per kilogram of body weight are shown in Fig 6 The administration of sotalol reduced heart rate cardiac output left ventricular work mean and stroke coronary flow with no change in stroke volume mean and late diastolic coronary resistance were increased The increase in heart rate cardiac output and left ventricular work produced by stress were significantly reduced after sotalol 1 0 mg per kilogram of body weight but were largely unaltered by 0 2 mg per kilogram of body weight The changes in mean and stroke coronary flow and in mean and late diastolic resistance in response to stress were also reduced by sotalol

Discussion

The changes in systemic and coronary hemodynamics induced by stress in the present experiments are similar to those previously reported in conscious dogs[3,4] Delivery of an auditory stimulus significantly increased heart rate cardiac output and left ventricular work peak blood pressure rises were always accompanied by slowing of the heart rate which is likely to depend upon baroreceptor reflex[11] Stroke and mean coronary flow were increased and coronary resistances were decreased

In the present experiments propranolol

prenolol also indicates that activation of beta adrenoceptors in the coronary vessels is involved in the physiological adaptation of the coronary circulation to a stressful situation

Summary

The present observations were made to investigate the role of beta adrenoceptors in the hemodynamic response to stress in conscious dogs Probes for electromagnetic flowmeter were implanted on the ascending aorta and left circumflex coronary artery and a catheter was inserted into the aortic arch 15 days before observations were made Emotional stress produced by firing a gun increased heart rate cardiac output and left ventricular work The responses were reduced by propranolol practolol and sotalol 0 2 and 1 0 mg per kilogram of body weight and abolished by alprenolol The difference between the effect of alprenolol and the other drugs may result from the marked intrinsic sympathomimetic activity of alprenolol which increased the resting level of heart rate cardiac output and left ventricular work

Emotional stress increased mean blood flow through the left circumflex coronary artery as a result of increase in stroke coronary flow and heart rate Propranolol sotalol and practolol reduced the increase in mean coronary flow produced by stress through a reduction in tachycardia the increase in stroke coronary flow was unaltered The decreases in mean and late diastolic coronary resistance produced by stress were not altered by these three drugs

Alprenolol unlike the other drugs completely abolished the increases in mean and stroke circumflex coronary flow and the decreases in coronary vascular resistance produced by stress

The present observations indicate that the dilatation of coronary arteries produced by stress does not result entirely from an increase in cardiac metabolism they also suggest that stimulation of beta adrenoceptors in the coronary arteries plays an important role in the coronary vasodilatation produced by emotional stress

The authors wi h to express their gr titude to the L ff members of the Cardiovascular Department of the Carlo Erba Institute for their individual contributions to this study

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vagus nerves and from an unknown mechanism

In contrast to the effects of propranolol, alprenolol, 1 mg per kilogram of body weight, abolished almost completely the increases in heart rate, cardiac output, and left ventricular work produced by stress. As the beta adrenoceptor blocking activity of propranolol and alprenolol is similar,[10] the difference in their effects on the response to stress would appear to result from other differences in their properties. Alprenolol has intrinsic sympathomimetic activity[10] which was apparent in the present experiments from the increases in resting levels of heart rate, cardiac output, and left ventricular work which it produced. As these increases were comparable to those produced by stress after propranolol 1 mg per kilogram of body weight, they may have masked the effects of stress after alprenolol 1 mg per kilogram of body weight so that the inhibitory effects of the two drugs on the responses to stress may not be different. Both practolol and sotalol have been shown to be less potent than propranolol in blocking beta adrenoceptors. The results obtained in the present experiments confirm these previous findings as the two drugs were less effective than propranolol in antagonizing the systemic hemodynamic response to emotional stress.

Although propranolol reduced the increases in heart rate and cardiac work in response to stress, it did not significantly alter the intrinsic response of the coronary vessels to stress. Although the increase in mean and left circumflex coronary flow was reduced by the drug as a result of a decrease in the heart rate response, stroke coronary flow response to stress was unaltered. This conclusion is supported by the observation that the decreases in mean and late diastolic coronary resistances produced by emotional stress were not altered by propranolol. Previous studies[7] have indicated that propranolol, although inhibiting the cardiac responses to stress in conscious dogs, did not alter the changes in the coronary circulation.

The effect of practolol was similar to that of propranolol. Sotalol significantly inhibited the increase in mean coronary flow and the reduction in mean and late diastolic coronary resistance produced by stress.

Alprenolol almost completely blocked the coronary vascular response to stress as indicated by the lack of variation in stroke coronary flow and in mean and late diastolic coronary resistance after administration of the drug. The concurrent blockade of the cardiac acceleration prevented mean coronary flow from increasing. The reason for the difference between the effects of alprenolol and those of propranolol, practolol, and sotalol is not clear. It does not arise from differences in the beta blocking activity of alprenolol and propranolol since the two drugs were equally effective in blocking the effects of isoprenaline on the coronary vasculature in conscious dogs.[10]

The difference in the effects of the two drugs on coronary hemodynamics could result from alprenolol being more effective in blocking the effects of endogenously released noradrenaline, although there are no other observations to support such a hypothesis.

Drugs which block beta adrenoceptors have been shown to inhibit the increases in cardiac work and oxygen consumption provoked by simulated exercise in anesthetized dogs[17] and by exercise in conscious dogs,[18] but there are no reports of the effect of these drugs on the hemodynamic and metabolic changes induced by stress. In the present experiments propranolol and alprenolol (1 mg per kilogram of body weight) reduced the increases in work and rate of heart produced by stress by 71 and 75 per cent, respectively. We did not measure the concurrent changes in oxygen consumption before and after beta blockade, but as a relationship between cardiac work, heart rate, and oxygen consumption has already been demonstrated by previous authors,[3, 12, 19] it can be assumed that in the present experiments the increases in oxygen requirement of the myocardium during stress were reduced to the same extent as the increase in cardiac work. The simultaneous observation that the coronary vasodilatation is unaltered by propranolol suggests that the changes induced by stress in the coronary circulation do not result entirely from an increase in myocardial metabolism. The blockade of the changes in coronary hemodynamics produced by al-

Case
reports

Cardiac lymphangioma and lipoma

Report of a case of simultaneous occurrence in association with lipomatous infiltration of the myocardium and cardiac arrhythmia

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In spite of an increased awareness and improvement of diagnostic techniques primary tumors of the heart are infrequently encountered The occurrence of multiple primary cardiac tumors is rarely reported and its incidence is unknown While primary cardiac tumors may produce a variety of symptoms cardiac arrhythmias are relatively common in patients with metastatic or malignant primary tumors They are less frequent in patients with benign primary tumors[1]

This case is reported because of the simultaneous occurrence of two distinct benign cardiac tumors One of these we believe contributed to the production of cardiac arrhythmias

Case report

A 43 year old Caucasian man was seen at the Henry Ford Hospital with a twenty year history of episodes of palpitations Although he had had a number of medical evaluations an etiology for the palpitations was never established Approximately three weeks prior to his referral to our hospital he was hospitalized elsewhere because of severe substernal chest pain This radiated into the left arm and fingers and was accompanied by dyspnea and diaphoresis The pain continued intermittently for several days During this time serial creatine phosphokinase (CPK) serum glutamic oxalacetic transaminase (SGOT) lactic dehydrogenase (LDH) determinations and electrocardiograms (ECG) were normal except for frequent premature ventricular contractions (PVC) and supraventricular tachycardias (Fig 1) The initial blood pressure was 1 0/110 mm with subsequent blood pressure being normal The patient and two of hi brothers were considered to have borderline diabetes

Physical examination at the Henry Ford Hospital revealed a well developed man in no acute distress with a blood pressure of 132/88 mm Hg The lateral border of cardiac dullness was 13 cm. from the midsternal line P_2 was greater than A_2 M_1 greater than M and the heart rate was 88 per minute Other findings of the physical examination were normal

Laboratory studies Chest fluoroscopy revealed slight cardiomegaly with no specific chamber enlargement Fasting blood sugar was 80 mg per cent two-hour postcibal (PC) blood sugar 105 mg per cent blood urea nitrogen (BUN) 11 mg per cent urinalysis within normal limits prothrombin time 13 sec with a control of 1? sec hemoglobin 14 7 Gm per cent white blood cells (WBC) 11 500 per cubic millimeter with 2 neutrophilic bands ?0 neutrophils 2 eosinophils 21 lymphocytes and 5 monocytes Venereal Disease Research Laboratory (VDRL) test nonreactive triglyceride 132 mg per cent uric acid 7 I mg per cent serum calcium 9 2 mg per cent serum phosphate 3 3 mg per cent serum complement 258 9 units total cholesterol 200 mg per cent Serum protein electrophoresis albumin 3 64 Gm per cent alpha 0 21 Gm per

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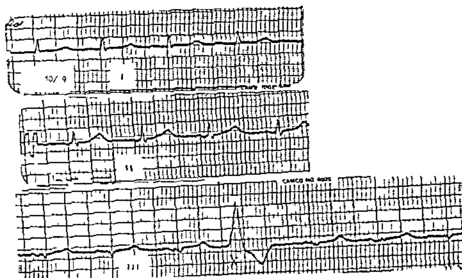


Fig 3 Leads I II III Pacemaker shifting from the sinus node to the junction best shown in Lead II

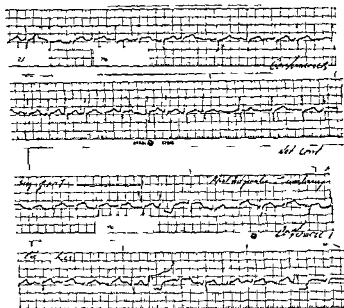


Fig 4 Monitor lead Atrial or sinus tachycardia with wandering pacemaker (inverted P wave of junctional beat)

base of the aorta the epicardium appeared gray firm and fibrous Transection through this area revealed a thick firm fibrous tissue containing a number of spaces 1 to ? mm in diameter

A discrete yellow moderately firm 2 6 by 2 1 by 3 cm nodule was present in the right atrial wall in the region of the Eustachian valve and coronary sinus It slightly distorted these two structures and protruded into the right atrial chamber (Figs 9 and 10) Cross sections through the nodule revealed it to be adipose tissue that was well delineated from the surrounding atrial wall Replacement of the myocardium by adipose tissue was diffuse and marked in the right atrium moderate in the right ventricle and minimal in the left atrium

Microscopic pathology The epicardium in the area of the entire A V sulcus and the adventitia of the root of the aorta were thickened by poorly cellular fibrous tissue which contained many empty variously sized tortuous channels (Figs 11 to 13) These

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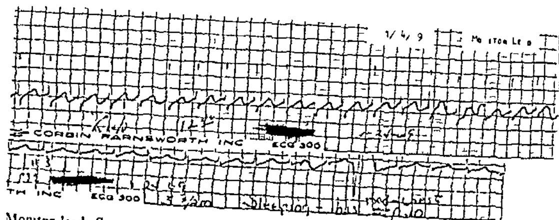


Fig 1 Monitor lead Supraventricular tachycardia suggestive of paroxysmal atrial tachycardia Occasional premature ventricular contraction

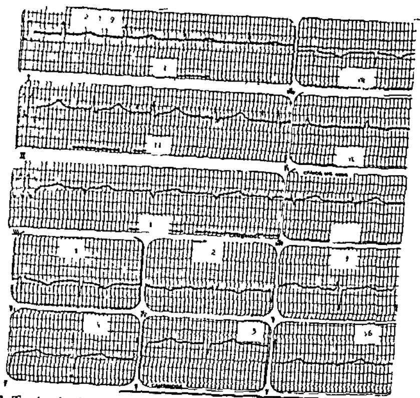


Fig 2 Twelve lead ECG Normal ECG except for a negative T wave in aV_L

cent alpha₂ 0 96 Gm per cent beta globulin 1 03 Gm per cent gamma globulin 1 14 Gm per cent total protein 7 0 Gm per cent SGOT *15 units* CPK 220 and 120 units LDH 485 and 505 units

Hospital course The initial ECG s revealed a basic sinus rhythm a negative T wave in aV_L occasional PVC s and many atrial premature contractions with evidence of a wandering pacemaker moving from the sinus node to the A V junctional area (Figs 2 and 3) After this four days of continuous ECG monitoring in the coronary care unit revealed evidence of a wandering pacemaker frequent premature atrial and junctional beats occasional ventricular premature beats periods of sinus tachycardia occasional short runs of supraventricular tachycardia which resembled paroxysmal atrial tachycardia (PAT) and a period of first degree A V block (Figs 4 to 6) The patient s chest pains subsided after the first hospital day On the ninth hospital day selective right and left coronary arteriograms were performed (Figs 7 and 8) Two injections of 4 ml of Renografin 75 were made into the right coronary artery and three injections into the left coronary artery Following the third injection of Renografin 75 into the left coronary artery there ensued hypotension bradycardia and subsequently cardiac arrest (asystole ventricular tachycardia ventricular fibrillation) Continued attempts at resuscitation for two hours and fifty minutes were unsuccessful Autopsy permission was obtained

Gross pathology The only significant autopsy finding was in the heart The heart weighed 650 grams with hypertrophy of the myocardium of both ventricles The valves were unremarkable and the coronary arteries showed only minimal atherosclerosis In the A V sulcus encompassing the entire heart and

I I me 86
N mb 2



Fig 7 Normal left coronary angiogram left anterior oblique projection



Fig 8 Normal right coronary angiogram left anterior oblique projection



Fig 9 The circumscribed tumor (A) of the interatrial septum distorts the Eustachian valve and coronary sinus Adipose tissue has replaced much of the muscle of the right atrium (B) right ventricle (C) and A V node (D)

atrial wall was an accumulation of fat cells with few interspersed cardiac muscle fibers The myocardial fibers of the walls of all the chambers were increased in size and contained large hyperchromatic nuclei Focal small areas of fibrosis were present in the left ventricular muscle

Discussion

A number of diagnostic interpretations are prompted by the composite of vascular spaces adipose tissue and smooth muscle diffusely distributed throughout both atrial walls and adventitia of the base of the aorta These include (1) malformation (hamartoma) of multiple mesenchymal tissues (2) lymphangioma associated with a marked adipose infiltration of cardiac muscle with the formation of a discrete tumor of adipose tissue of the right atrial muscle

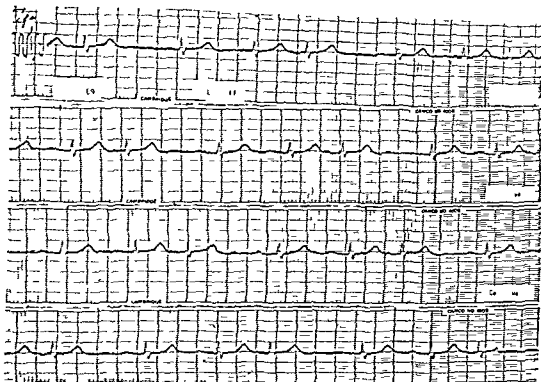


Fig 5 Long Lead II First degree A V block with PR of 0 22 sec Premature atrial contractions with atrial trigeminy Note that the atrial premature beats have a shorter PR interval of 0 16 sec

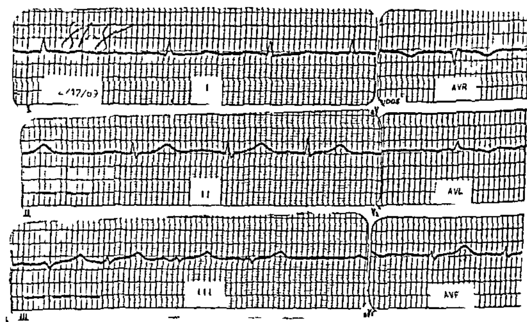


Fig 6 Junctional tachycardia in Lead III

channels were lined by uniform flat endothelial cells and had walls of thin fibrous tissue or fibrous tissue with smooth muscle that were focally thickened Although irregularly arranged thin elastic fibers were present in some of the larger channels no internal or external elastic lamina could be found Similar endothelial lined channels variously sized nerves bundles of smooth muscle and adipose tissue replaced most of the muscle of the right atrium and interatrial septum and to a lesser extent the muscle of the left atrium Muscle replacement by adipose tissue was diffuse and very extensive in the right atrium in the atrial septum and in the sinoatrial and A V nodes (Fig 14) It was moderate in the right ventricle and minimal in the left atrium The sections did not include the bundle of His Distant from the A V sulcus the epicardium of the atria and right ventricle was not fibrotic but contained increased adipose tissue This tissue was in continuity with the fat cells in the underlying cardiac muscle and often was not accompanied by the endothelial lined channels The polypoid nodule in the right



Fig 7 Normal left coronary angiogram left anterior oblique projection



Fig 8 Normal right coronary angiogram left anterior oblique projection



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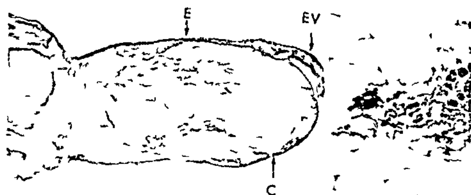


Fig. 10. (A left) Section through the tumor (A of Fig. 9). It is differentiated adipose tissue replacing most of the cardiac muscle fibers. EV, Eustachian valve; E, endocardium of right atrium; C, endothelial surface of roof of the coronary sinus. (Hematoxylin and eosin, 2.6×.) (B right) Magnification of an area of (A). (Hematoxylin and eosin, 175×.)

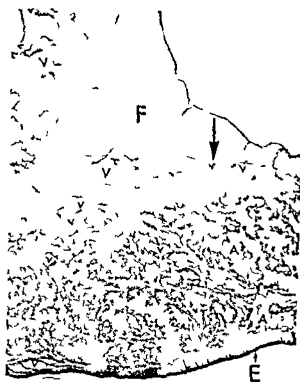


Fig. 11. Full thickness section through the left atrial wall and A-V sulcus. Many empty channels (V) and adipose tissue (A) are diffusely distributed throughout the atrial muscle to the subendocardial area. Poorly cellular fibrous tissue (F) is found principally in the epicardium replacing the adipose tissue. E, Left atrial endocardium. (Hematoxylin and eosin, 7.5×.)

and (3) a mixed mesenchymal neoplasm (benign mesenchymoma). A lymphatic rather than a blood vascular growth is indicated by (1) the absence of a well developed muscle coat with internal and external elastic lamina in the channels that would be expected in veins and arteries of comparable size, (2) failure to demonstrate a vascular abnormality in the coronary arteriogram, (3) absence of blood in the endothelial lined channels, and (4) the histologic similarity between the cystic lymphangioma (hygroma) occurring in other areas and the present growth.

Eleven cardiac tumors composed of more than one type of mesenchymal tissue—adipose, vascular, and smooth muscle—have been reported.[2-4] Depending on the author's views regarding neoplasia and malformation, the terms hamartoma, benign mesenchymoma, lymphangioma, or an elaborate descriptive diagnosis have been used. Unlike the case under discussion, seven of the tumors were discrete masses. Six involved the epicardium and one involved the myocardium of the right ventricular outflow tract. Four tumors were diffuse, involving the left ventricular myocardium in two instances, the myocardium of both ventricles in one case, and the A-V node in the fourth case. In five cases the tumors did not produce symptoms and were discovered at necropsy or as a cardiac enlargement in a routine chest x-ray. Dyspnea, chest pain, systolic cardiac murmur, palpitations, and pericardial effusion were present singly or in combination in four of the cases and heart block was present in one case. Successful surgical removal of the tumor was possible in five cases.

The microscopic descriptions and photomicrographs indicate that there are two tumor types among these 11 cases which differ primarily in their vascular makeup. In one group the vessels are large with a well formed muscle coat and elastic lamina



Fig 12 (A left) Area of Fig 11 (arrow) magnified (Hematoxylin and eosin 70X) (B right) Some of the smooth muscle bundles (M) not forming part of the channels are depicted (Hematoxylin and eosin 240X)



Fig 13 (A left) The adventitia (A) of the aorta (AO) is thickened by fibrous tissue which contains many lymphatics (V) in addition to the normal blood vessels and adipose tissue (Orcein azure eosin stain 13X) (B right) Area of (A) (arrow) magnified A Adipose tissue V lymphatic channels (Orcein azure eosin stain 70X)

while in the other group they are predominantly small with little or no muscle coat It appears that the former are best classified as arterial and/or venous malformations (hamartomas) and the latter as lymphangiomas The case of the present report is considered another example of diffuse lymphangioma with the added feature of

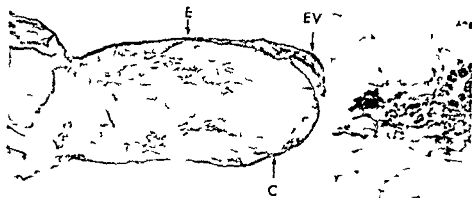


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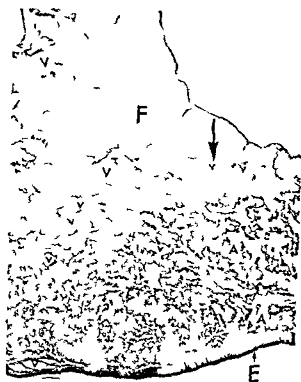


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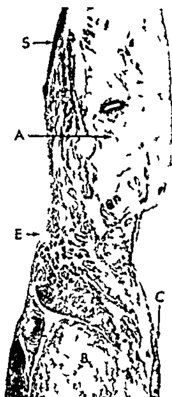


Fig 14 Adipose tissue has replaced most of the muscle of the sinoatrial node (*A*) and right atrial wall (*B*) The epicardium at the A V sulcus is thickened by fibrous tissue (*C*) *S* Superior vena cava *E* endocardium of right atrium (Hematoxylin and eosin 6 5X)

both a localized and diffuse lipomatous infiltration of the myocardium, the former representing a lipoma A lymphatic vascular origin rather than a blood vascular origin is supported by the failure to visualize the tumor in the angiocardiographic studies of one of the reported cases and by the coronary arteriogram in the present case

The controversial question of neoplasm vs malformation for this type of growth and the relationship of the localized and diffuse lipomatous change in the cardiac muscle to the lymphangiomatous changes are not resolved by this study The diffuse and localized lipomatous changes are not uncommon in the right atrial and atrial septal muscle and could represent a fortuitous association with the lymphangioma or an integral part of a malformation or a benign neoplasm [13] The degree of lipomatous myocardial change is unusual in relation to the patient's age, normal body weight, and the absence of a similar alteration in other organs Its presence in the right ventricular and atrial muscle unassociated with the lymphatic channels suggests that it is independent of the lymphangioma

Whether one considers this type of growth a hamartoma, benign mesenchymoma or a lymphangioma is less important than the recognition of its nonmetastasizing character, variability of its local behavior, diffuse epicardial and myocardial involvement, and discrete solitary tumorlike growth Although the degree of epicardial fibrosis was unusual, it should be differentiated from a myocardial fibroma which has been occasionally designated as a hamartoma

A casual relation between the cardiac muscle replacement and interruption of conduction system tracts and the clinical manifestations referable to the heart is strengthened by the failure to demonstrate significant coronary artery or myocardial disease by coronary arteriogram and tissue examination Marked cardiac tissue replacement in the region of the sinoatrial node A V node and bundle of His has been associated with sinus bradycardia atrial tachycardia sinus arrests junctional beats atrial fibrillation premature atrial beats and conduction abnormalities The infiltrating tissue has variously been mesothelioma angioma lipoprotein and fat as in cases of lipomatous infiltration of the interatrial septum [4 13 19]

In the case presented here there was replacement and interruption of cardiac muscle in vital areas by a variety of tissues—adipose vascular smooth muscle and fibrous We believe that the conduction system disturbance can be attributed to these changes

Summary

Multiple supraventricular arrhythmias in a 43 year old man are attributed to the interruption and replacement of the specialized muscle of the conduction system The morphologic appearance of the vascular channels and their failure to fill in the coronary arteriogram indicate that the channels are of a lymphatic origin and that the growth is one of a diffuse lymphangiomatous

process associated with a lipomatous replacement of atrial cardiac muscle which in one area formed a discrete tumor a lipoma

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Propranolol-induced alopecia

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Propranolol hydrochloride has gained widespread clinical usage for a variety of cardiovascular disorders. It is generally a well tolerated drug, but a variety of undesired effects, unrelated to its pharmacologic effects, have been observed. These include mental confusion, nausea, vomiting, diarrhea, palpitations, rashes, sleeplessness, fatigue, and light-headedness.[1] Three instances of reversible alopecia coincident with propranolol hydrochloride administration were reported during the clinical investigation of the drug.* However, direct relationship of the alopecia to the administration of the drug was not established. The following report describes an instance of reversible alopecia secondary to administration of propranolol hydrochloride in which the causal relationship is strongly suggested by drug re-challenge.

Case report

A 36-year-old man developed supraventricular tachycardia in 1959 and was diagnosed as having the Wolff-Parkinson-White syndrome in 1962. At that time he was treated with digoxin, quinidine, and procainamide. Over the ensuing years he had recurrent episodes of supraventricular tachyarrhythmias and was treated with a variety of drugs in addition to those mentioned above, including reserpine, guanethidine, hydroxazine, and diphenylhydantoin. He was unresponsive to these medications as well as to induction of hypothyroidism with methimazole, stellate ganglion block, and paired atrial stimulation. In 1965 he had a two-month trial of therapy with propranolol hydrochloride in a dose ranging from 10 mg. to 30 mg. four times daily. Again in 1967 he had a three month trial with propranolol in similar doses. On each occasion there was little response of his arrhythmia, but on neither occasion was alopecia noted.

In September, 1970, he was again started on propranolol hydrochloride, 10 mg. twice daily. Additional medications at that time included gitalin and quinidine. Over the next three months the dose of propranolol hydrochloride was increased to 40 mg. four times daily. In January, 1971, he noted for the first time a patchy hair loss involving his scalp, chest, and arms. This alopecia progressed slowly until May, 1971, when the process seemed to suddenly accelerate. In June, 1971, he consulted his physician and the propranolol hydrochloride was discontinued. At that time there were patchy areas of hair loss over the scalp and arms (Fig. 1) and centrally diffuse hair loss from the chest (Fig. 2). The underlying skin appeared normal.

Telogen counts from the periphery of the bald areas of the scalp averaged 68 per cent (normal scalp averages 15 per cent telogen hairs[2] and telogen counts over 25 per cent are diagnostic of telogen effluvium[3]). A biopsy of the scalp in an area of alopecia was normal except for the increased number of telogen hairs.

Microscopic examination of scalp and body hairs

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*Harvey A. Barnett, M.D., Assistant Medical Director, Ayerst Laboratories, N. Y., in a letter to Doctor Martin dated October 11, 1971.

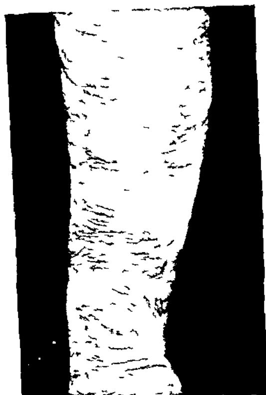


Fig *1* The patient s arm showing diffuse patchy alopecia.



Fig *2* The patient s chest showing a central more diffuse hair loss.

removed by gently pull ng hairs from the periphery of the bald patches revealed normal appearing telogen and anagen hairs However with polarized l ght m croscopy the telogen hair bulb were noted to be dy plastic and the e was a dy pla tic defect in each of these ha r hafts about one third distal from the bulb Anagen hairs appeared normal under polarized l ght microscopy

The alopecia progressed over the next two months until he had extens ve hair loss from his chest fore arm a d eyebrows and approximately 50 per cent loss from hi scalp By the end of the fourth month after d scontinuing p opranolol hydrochloride he had al most complete resolution of the alopecia At th s time after nformed consent had been obtained he was re-challenged with propranolol hydrochloride 0 mg four times daily W thin four weeks he had defin te recurrence of the alopecia again beginning on the scalp chest and forearms The shed hairs were telogen Prop anolol hydrochlor de was again d scontinued and over the next four months he had grad al and complete return of his ha r growth

Comment

Drug induced alopecia is characteristi cally the anagen effluvium type The drug acts on the hair follicle to inhibit mitosis Examples of drugs that cause this type of alopecia are the antimitotic agents folic acid antagonists purine antagonists alky lating agents thallium and colchicine

Telogen effluvium following drug therapy is rarely reported except for heparin in duced alopecia This is an unusual case of telogen effluvium with dysplasia of the hair bulb and hair shaft caused by pro pranolol

The criteria of Kligman[3] for telogen effluvium—i e (1) huge telogen counts—25 per cent to 60 per cent (2) latency period of about 3 months between stress and shedding (3) loss of club hairs from normal telogen follicles and (4) regrowth with drug cessation have been fulfilled Also when re-challenged with the drug there was re currence of hair loss The re-challenge showed that the drug induced telogen hair loss occurred more rapidly (one month) than that seen with stress induced (fever etc) telogen effluvium

Summary

A patient developed diffuse patchy alo pecia following propranolol therapy This was reproduced by re-challenge with the drug The alopecia demonstrated the cri teria for telogen effluvium

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Propranolol induced alopecia

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Propranolol hydrochloride has gained widespread clinical usage for a variety of cardiovascular disorders. It is generally a well tolerated drug, but a variety of undesired effects unrelated to its pharmacologic effects have been observed. These include mental confusion, nausea, vomiting, diarrhea, palpitations, rashes, sleeplessness, fatigue, and light headedness.[1] Three instances of reversible alopecia coincident with propranolol hydrochloride administration were reported during the clinical investigation of the drug.* However, direct relationship of the alopecia to the administration of the drug was not established. The following report describes an instance of reversible alopecia secondary to administration of propranolol hydrochloride in which the causal relationship is strongly suggested by drug re-challenge.

Case report

A 36-year-old man developed supraventricular tachycardia in 1959 and was diagnosed as having the Wolff-Parkinson-White syndrome in 1962. At that time he was treated with digoxin, quinidine, and procainamide. Over the ensuing years he had recurrent episodes of supraventricular tachyarrhythmias and was treated with a variety of drugs in addition to those mentioned above, including reserpine, guanethidine, hydroxazine, and diphenylhydantoin. He was unresponsive to these medications as well as to induction of hypothyroidism with methimazole, stellate ganglion block, and paired atrial stimulation. In 1965 he had a two-month trial of therapy with propranolol hydrochloride in a dose ranging from 10 mg. to 30 mg. four times daily. Again in 1967 he had a three month trial with propranolol in similar doses. On each occasion there was little response of his arrhythmia, but on neither occasion was alopecia noted.

In September 1970 he was again started on propranolol hydrochloride, 10 mg. twice daily. Additional medications at that time included gitalin and quinidine. Over the next three months the dose of propranolol hydrochloride was increased to 40 mg. four times daily. In January 1971 he noted for the first time a patchy hair loss involving his scalp, chest, and arms. This alopecia progressed slowly until May 1971, when the process seemed to suddenly accelerate. In June 1971 he consulted his physician and the propranolol hydrochloride was discontinued. At that time there were patchy areas of hair loss over the scalp and arms (Fig. 1) and centrally diffuse hair loss from the chest (Fig. 2). The underlying skin appeared normal.

Telogen counts from the periphery of the bald areas of the scalp averaged 68 per cent (normal scalp averages 15 per cent telogen hairs[2] and telogen counts over 25 per cent are diagnostic of telogen effluvium[3]). A biopsy of the scalp in an area of alopecia was normal except for the increased number of telogen hairs.

Microscopic examination of scalp and body hairs

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*Harvey A. Barnett, M.D., Assistant Medical Director, Ayerst Laboratories, N.Y., in a letter to Doctor Martin dated October 11, 1971.

Table I Patient data on July 9 1971

Time (A M)	*Location*	*Systolic pressure*	*Diastolic pressure*	*Mean*	*Rhythm*	*Heart rate*
9 48	AO	115	73	90	AF	110
	PA	63	26	41		
10 10	Hypotension					
10 29	AO	13	70	97	AF	110
	PA	61	24	38		
	RA	C = 17	V = 22	14		
10 44	LV	107	16 20			
	RPCW			29		
	RPA	35	24	28		
	RA			19		
10 47	LV	102	15 20			
	AO	100	71	74		
	PA	35	25	29		
	RV	35	15 20			
	RA			20		

Abbreviations AO = aorta PA = pulmonary artery RA = right atrium RV = right ventricle LV = left ventricle RPCW = right pulmonary artery wedge RPA = right pulmonary artery C = C wave V = V wave AF = atrial fibrillation.

the patient lying in bed propped up at a 30 degree angle The chest expanded fully and symmetrically and an occasional wheeze was heard Coarse rales were noted at the left base and minimal râles were noted at the right base The peripheral pulses were equal in intensity and graded as 2+ for the carotids radials and femorals Dorsal pedal pulses were not palpable bilaterally Examination of the heart revealed an irregular rhythm with a heart rate of 120 per minute Paradoxical pulsations were noted over the apex There was a loud S 3 A Grade III/VI systolic murmur and a Grade II/VI mid-diastolic rumble were heard at the apex The holosystolic murmurs radiated into the axilla The liver and spleen were not palpable A large reducible inguinal hernia was seen on the right Rectal examination was within normal limits Neurological examination was unremarkable Examination of the extremities revealed 4+ pitting edema over the feet and tibiae

Laboratory data and hospital course Chest x ray was read as showing marked cardiomegaly predominantly left atrial enlargement with clear lung fields showing no active infiltration ECG revealed abnormalities due to atrial fibrillation non specific ST T wave changes and an occasional aberrantly conducted beat Vectorcardiography was reported to be abnormal due to left ventricular hypertrophy with probable septal hypertrophy and abnormal T waves probably secondary to left ventricular hypertrophy Urinalysis on admission was within normal limits Hemoglobin was 14 6 Gm per 100 c c hematocrit was 44 5 per cent white blood cell count was 9 400 per cubic millimeter with 80 per cent neutrophils 19 per cent lymphocytes 1 per cent monocytes adequate platelets with a few ovalocytes and microcytes and a few bizarre target cells SMA-6 was within normal limits except for a glucose of 165 mg per cent prothrombin time was 11 4 seconds Venereal Disease Research Laboratory test was non reactive On July 9 the patient was sent for cardiac catheterization During this procedure as the transseptal puncture was attempted the patient became hypotensive and dyspneic The hypotensive episode lasted from 10 00 A M to 10 20 A M with mean aortic pressure ranging from 70 to 75 mm mercury Following this pressures from the aortic root pulmonary artery and right atrium were again recorded Because of progressive dyspnea of the patient the study was interrupted However the following information (Table I) was recorded

Following return to the ward the patient remained hypotensive with a systolic pressure of 75 to 80 mm Hg It was noted that there was no urine output and that the urinary bladder was not distended A Foley catheter was passed but no urine was drained At 10 45 P M on July 9 1971 the patient was transferred to the Intensive Care Unit and an intra arterial line was placed in the left arm A central venous pressure line (CVP) was placed in the right arm At the time of admission to the Intensive Care Unit the blood pressure was 100/80 pulse rate 120 per minute Wheezes were noted in the anterior lung fields and râles were observed in the posterior lung field The liver was noted to be 4 fingerbreadths below the costal margin in the mid clavicular line The spleen was not palpable Levophed was administered by drip until the blood pressure was stabilized The laboratory tests were reported as sodium 139 mEq per liter potassium 5 6 mEq per liter chlorides 99 mEq per liter carbon dioxide measured 17 blood urea nitrogen 39 mg per cent glucose 130 mg per cent creatinine 2 9 mg per cent calcium 5 2 mEq per liter The nephrologist in consultation thought that the patient had acute tubular necrosis He had no response to large doses of Lasix and was treated for renal failure with restriction of fluid

On the evening of July 10 1971 it was noted that the patient had large ecchymoses at several venous puncture sites and at the site of the right brachial

Clinical pathologic conference

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Case report

Clinical abstract. This was the first admission to the University of Illinois Hospital for this [illegible]9 year old Caucasian man. He was referred from an outside hospital with a diagnosis of arteriosclerotic heart disease and left ventricular aneurysm.

The patient first complained of dyspnea and weakness of sudden onset in 1956. He was hospitalized at that time and placed on digitalis and water pills. He was then asymptomatic until 1963 when he was again hospitalized for retention of fluid. No further information could be obtained with respect to these two hospitalizations or his condition subsequent to the second one. However, it is known that he was hospitalized for a third time on June 7, 1966, because of considerable increase in dyspnea and orthopnea. There had been no peripheral edema or angina. The patient was diagnosed as having arteriosclerotic heart disease with auricular fibrillation and congestive failure. He was given diuretics and placed on digitalis. He was discharged on June 17, 1966, greatly improved and in cardiac compensation.

The patient's next admission, the fourth hospitalization since 1966, was on June 4, 1971, due to nausea, vomiting, and weight loss for one week. He had been maintained on Lanoxin and Hygroton.

Physical examination at the outside hospital revealed pulse 100, cardiac respirations 22, blood pressure 130/82. There was an irregular rhythm. A 2 was louder than P 2. There were no particular murmurs or extrasystoles. The liver was one finger breadth below the right costal margin. An electrocardiogram (ECG) was reported to have shown auricular fibrillation and incomplete left bundle branch block.

X-ray study of the chest was reported by the radiologist as follows: Preliminary fluoroscopy of the chest shows a markedly enlarged heart. Along the left heart border there are two densities. One, the main density, pulsates as the heart beats normally. The other density, which is anterior to it, also has a rounded contour, is separate from the main density, and is not as dense. It probably represents a large aneurysm along the anterior ventricular wall covering a distance of at least 6 by 7 cm. In addition to this, on barium swallow the esophagus is deviated markedly to the right and is elevated at the level of the arch of the aorta in a manner typical of an enlargement of the left auricle. So this patient must have some type of mitral valvular defect besides the aneurysm to cause the marked enlargement of the left auricle.

For this reason the patient was transferred to the University of Illinois Hospital for further evaluation and treatment on June 25, 1971. The following pertinent information was elicited. He never had chest pain, palpitation, or hemoptysis. He gave no history which could be interpreted as that of rheumatic fever, but he did give a history of gouty arthritis. He had smoked one pack of cigarettes a day for the past 45 years.

He had had an appendectomy in 1943, herniorrhaphy in 1948, and cholecystectomy in 1955.

Physical examination. Examination revealed a healthy appearing elderly Caucasian man in no acute distress. Blood pressure was 130/80 mm. mercury. Pulse rate was irregularly irregular ranging from 90 to 130 per minute; temperature was 98.6° F. The skin was flaccid and dry with seborrheic keratoses about the face. The head was normocephalic. The pupils were equal, round, and reactive to light and accommodation. Funduscopic examination revealed mild arteriovenous nicking, copper wire changes, and arteriolar narrowing. The tympanic membranes were clear. There was a mild hearing deficit. Examination of the neck revealed distended veins for a distance of 4 cm. above the clavicle with

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The physical examination now done at the University hospital reveals a normal blood pressure an irregular pulse retinal changes which would be consistent with either arteriosclerosis or pre existing hypertension The neck veins were distended consistent with the diagnosis of cardiac failure but the pulsations are not described It would be interesting to know if there were large systolic pulsations or whether the neck veins were distended and without pulsations The former would suggest the presence of tricuspid insufficiency the latter might suggest obstruction to filling of the right heart either by a lesion in the mediastinum pericardial effusion or loss of compliance of the right ventricle The absence of pedal pulses is further evidence of the patient s generalized arteriosclerosis We are now told that there is paradoxical pulsation over the apex of the heart and this I assume means that there are two impulses pulsating asynchronously as one would see with a ventricular aneurysm Up till this point we are essentially told that the patient has a ventricular aneurysm and the findings so far are consistent with this diagnosis I should point out that other diagnoses are possible such as pericardial cyst or cardiac tumor to explain the x ray shadow which has been described Pericardial cysts usually appear at the right lower cardiac border although they can appear anteriorly and they can be thought to pulsate paradoxically Cardiac tumors are less frequent in this age group Left atrial myxoma has to be considered It can produce mitral insufficiency However in the absence of embolic phenomena and fainting spells due to sudden episodes of obstruction I would be inclined to exclude that diagnosis I mention myxoma not only because the obscure becomes the common in this CPC exercise but also because the patient has mitral insufficiency and a murmur described in this hospital which was not described in the other hospital immediately before transfer Mitral insufficiency of course can cause a left lower sternal border lift and with this in addition to the apical pulsation may give the appearance of paradoxical motion The left lower sternal lift is due to the regurgitant flow filling the left atrium ballooning the left atrium thus pushing the heart forward against the anterior chest wall In this hospital examination of the heart revealed a loud third sound Grade 3/4 systolic murmur and a Grade 2/6 mid-diastolic rumble at the apex I assume since the murmur is at the apex that the systolic murmur is holosystolic or plateau in character and that the third sound is coming from the left ventricle This all goes with the diagnosis of mitral insufficiency but also goes with the diagnosis of ventricular aneurysm with or without mitral insufficiency The systolic murmur described in ventricular aneurysm is usually due to a degree of mitral insufficiency but this does not have to be severe and the mid diastolic rumble merely represents the refilling of the left ventricular cavity from the aneurysm as well as the left atrium The loud third sound is evidence of volume overload at the left ventricle We now have physical findings to explain the failure either on the basis of a ventricular aneurysm or on the basis of mitral insufficiency The mid diastolic rumble could represent the filling rumble of severe mitral insufficiency or could represent the rumble appearing in ventricular aneurysm Also a loud third sound is consistent with either severe mitral insufficiency or ventricular aneurysm

The liver and spleen are not palpable This makes me a little uncomfortable as to what has happened to the liver The patient has rather severe pitting edema of his lower extremities I would expect that unless the patient has cirrhosis that his liver should be enlarged

We are now treated to further information from the ECG laboratory The vectorcardiogram is reported showing left ventricular hypertrophy but there is no mention of a myocardial infarct This makes me extremely uncomfortable with the diagnosis of ventricular aneurysm In the absence of bundle branch block ventricular aneurysms are almost always associated with evidence of previous myocardial infarction This is particularly true if the aneurysm lies on the anterior wall which is the description which has been given to me so far The rest of the laboratory examination does not particularly help me except for the fact that there is evidence of diabetes in one elevated glucose determination This of course would be even more sup

Table II Patient data on July 5 and on July 10 1971

Date	Hemoglobin (Gm per cent)	Hematocrit (volumes per cent)	White blood count (per mm³)	Platelets (per mm³)	Prothrombin (sec)
7 5 71	14 6	44 5	9 400	Adequate	11 4
7 10 71	11 6	33 7	24 300	74 000	25 8

cutdown Repeat and previous hematologic examinations revealed the following (Table II) findings

Fibrinogen was 201 mg per cent Split fibrin products were positive at 1 to 16 Partial thromboplastin time was 72 8 seconds The hematologist in consultation felt that the patient possibly had disseminated intravascular coagulation and recommended treatment with heparin should the patient continue to deteriorate On July 11 1971 it was noted that the patient had a low grade fever A smear of the sputum revealed gram positive diplococci The patient was then started on procaine penicillin 600 000 units intramuscularly every 12 hours It was necessary intermittently to stabilize the patient s blood pressure with Levophed Blood cultures drawn at the time of the elevated temperature were reported positive for gram positive cocci which were later identified as *Staphylococcus aureus* sensitive to penicillin G The patient accordingly was placed on nafcillin On July 12 1971 the patient remained oliguric with a temperature of 102° F and blood urea nitrogen of 84 mg per cent On July 13 1971 heparin therapy was begun with 10 000 units stat and 7 500 units every 4 hours The patient continued to deteriorate with periods of apnea and persistent coma Chest x ray revealed an infiltrate in the left lung He was intubated and placed on an MA 1 respirator He had an episode of nodal rhythm which was attributed to digitalis toxicity Digitalis was then withheld On July 14 1971 the patient could no longer breathe spontaneously without the assistance of a respirator Blood pressure was 34/20 pulse 70 at 8 15 P M All vital signs ceased at 8 45 P M

Discussion

DR GUNNAR The patient is a 79 year old man who was referred from another hospital with the diagnosis of arteriosclerotic heart disease and left ventricular aneurysm He first had evidence of cardiac failure in 1956 and this responded quite well to usual modes of treatment This episode was of sudden onset but unassociated with chest pain The patient did well until 1963 when he had another episode of failure, again treated successfully In 1956 he had evidence of left heart failure and at this time atrial fibrillation was first noted His final admission was June, 1971, with evidence of nausea, vomiting and weight loss This was attributed to digitalis and diuretic therapy

The description of the physical examination at the hospital before transfer to the University hospital shows a normal blood pressure evidence of atrial fibrillation and some evidence of cardiac failure The ECG at that time was described as showing in complete left bundle branch block which could mean several things One could assume that the ECG loop would be such that it would produce a loss of q waves over the left precordial leads and slurring of the upstroke of the left precordial leads This could be produced by left bundle block which has no initial rightward force The initial force quickly moves posteriorly and the loop moves in a clockwise direction in a horizontal plane A similar pattern could be produced by severe left ventricular hypertrophy where the loop assumes a figure of eight configuration with the initial rightward septal forces being obliterated by the strong forces from the posterior basal portion of the left ventricle The third possibility could be anterolateral infarction where the initial anterior forces may go clockwise initially and the entire loop rotates clockwise Which of these pertain may become apparent when we see particularly the vectorcardiogram

X ray studies done at the other hospital showed an enlarged heart and a very interesting description of a double density over the anterior wall of the left ventricle as well as evidence of left atrial enlargement The conclusion from the fluoroscopy was that the patient had mitral valve disease as well as a ventricular aneurysm We are given the additional information that the patient had a past history of gouty arthritis and a long history of smoking Both of these are risk factors for the appearance of arteriosclerotic heart disease

the fibrinogen level is at the lower limits of normal the split products were positive and the partial thromboplastin time was prolonged All of the e would be consistent with the diagnosis of disseminated intra vascular coagulation and this was the diagnosis made by the hematologist who recommended treatment with heparin This is indeed a difficult problem since we have a situation in which we have made the diagnosis that the patient had had a perforation of the heart at the time of catheterization with bleeding of the peri cardium and now two days later because of diffuse intravascular coagulation hepa rin is needed to block the process This is obviously the operation of Murphy s law which states that when anything can go wrong it will but I am afraid that with this patient no matter what decision is made it will be wrong I have of course the distinct advantage over the physicians treating this patient in that I know that the presentation of this patient in this amphi theater indicates that the therapy instituted was certainly not classified as a success

Gram negative bacteremia is much more prone to cause the diffuse intravascular coagulation since endotoxin release causes activation of Hagemann factor which in turn activates the coagulation cascade as well as activating the kinin system to cause vasodilatation and rather early cardiovascular collapse On July 11 the patient had a low grade fever and although the sputum revealed pneumococci a blood culture was positive for *Staphylococcus aureus* He was treated with penicillin G and later nafcillin We are not told whether or not this was a single culture or whether the staphylococcus was coagulase positive If this was a repeated positive culture for *Staphylococcus aureus* coagulase positive I would postulate (1) that it could have been induced by the cardiac catheter even though *Staphylococcus aureus* can be in troduced by urinary catheter and (2) that there was some mediastinal abscess which had been disturbed during the time of trans septal catheterization It appears that the patient continued to do poorly and died five days after the catheterization had been performed I now have the task of making a final conclusion I think I must make two diagnoses One for the situation prior to and the other for the condition after cardiac catheterization I would think that the most likely diagnoses prior to catheterization are arteriosclerotic heart disease previous myocardial infarction mitral insufficiency perhaps due to papil lary muscle dysfunction or even disruption of the chordae tendineae and less likely although possibly a ventricular aneurysm My discomfort with the diagnosis of ven tricular aneurysm is based on the lack of ECG information My diagnosis after catheterization would be that the patient had pericardial tamponade secondary to perforation of the atrium at the time of trans septal catheterization and that he developed gram negative bacteremia and diffuse intravascular coagulation subse quent to insertion of a Foley catheter The only way I can make a unified diagnosis would be to state that the patient did have a ventricular aneurysm and that the staphylococcal bacteremia was pre existent to his final hospitalization that he had endocarditis involving the mitral valve thus producing mitral insufficiency and that the resurgence of his bacteremia caused diffuse intravascular coagulation and his ultimate death

DR HOFFMANN * The chest film taken in the outside hospital prior to the present admission reveals a transverse cardiac diameter of 19 5 cm The heart shows generalized enlargement based on the single PA film The lung fields show pul monary venous hypertension with some redistribution of blood flow to the upper lung fields There are faint Kerley lines The views of the heart with barium in the esophagus indicate enlargement of at least the left atrium and ventricle

Six additional films were obtained during the present admission Cardiac catheteriza tion was performed on July 9 1971 On this day the transverse cardiac diameter was 22 0 cm This apparent increase in the silhouette can be explained by increased magnification when films are taken antero posteriorly with the patient in the supine position A central venous catheter was within the superior vena cava and marked enlargement of the left atrium was made apparent by considerable elevation of the

*Cardio scul r radiol g t

portive of the diagnosis of ventricular aneurysm since it is more common in the diabetic where silent infarction is more common It is not uncommon to have aneurysms appear in patients who do not have documented episodes of myocardial infarction Cardiac catheterization was performed on July 9 and the results of the catheterization are presented in the Table (Table I) The patient had an episode of hypotension shortly after an attempt was made to cross the atrial septum with a needle The blood pressure fell to 70 to 75 mm Hg, but after the needle was withdrawn the left heart systolic pressure returned to near normal levels It is unfortunate that we do not have a measurement of the right atrial pressure before the episode of hypotension The most common complication of trans septal catheterization of the left atrium is perforation of either the right or left atrium into the free pericardial cavity and occasionally there is puncture of the root of the aorta since the aorta lies in the upper portion of the atrium As we note the right ventricular systolic pressure fell and the mean left atrial pressure went from 14 to 20 The end diastolic pressures in the left ventricle and in the right ventricle were also 20 and these findings would be consistent with pericardial effusion and tamponade Since all four chambers of the heart are within the distended tense pericardium the end diastolic pressures in all four chambers tend to equalize There evidently was no attempt to do pericardiocentesis and the patient was returned to the ward still somewhat hypotensive After transfer to the Intensive Care Unit, the blood pressure was stabilized at 100/80 with a rapid pulse rate of 120 There were wheezes noted in the lungs The liver was described as four fingerbreadths below the costal margin The patient required Norepinephrine drip to stabilize his blood pressure but he was gradually taken off this medication Norepinephrine may not be the agent of choice in patients with pericardial tamponade even for a short period of time to stabilize their blood pressure since this agent tends to increase the end diastolic volume An agent which would tend to increase output at a smaller diastolic volume might be a more effective agent The best agent for this would be isoproterenol, but in a patient who is 76 years old with coronary artery disease there is a risk in using isoproterenol since it may lower perfusion pressure of the coronary arteries and increase myocardial ischemia The fact is, if the patient is hypotensive because of pericardial tamponade, then the treatment does not lie in the use of any of these agents but rather in aspiration of the pericardial effusion or pericardial blood It is somewhat difficult to aspirate much blood from these patients since the bleeding is rather vigorous and clotting occurs rather promptly within the pericardial cavity However, removing small amounts of fluid may relieve the tamponade sufficiently to allow time to decide whether or not surgical evacuation is or is not the treatment of choice If there is a good deal of blood in the pericardial cavity, this in my opinion, should be evacuated since this is an excellent stimulant for the formation of pericardial fibrosis and later development of constrictive pericarditis Subsequent to the episode of hypotension the patient developed renal failure thought to be due to acute tubular necrosis On July 10 the patient was noted to have ecchymoses at several puncture sites and at the site of the cutdown This is one day after the catheterization At this point there is a decrease in hemoglobin noted and although elevation of temperature is not recorded there is an elevation of white count to 24 300 decrease in the platelets to 74 000 and a decrease in the prothrombin time to 25 8 seconds All of these findings could be due to diffuse intravascular coagulation and the question arises as to the etiology Of course the most common reason is sepsis and the obvious source would be the cardiac catheterization However this is a very rare complication of cardiac catheterization so those of us who are familiar with this feature would look for other sites of sepsis My inclination would be to look at another catheter—the Foley catheter which was inserted into the bladder after the patient developed his shock like state This is a common source of gram negative sepsis and as we demonstrated at this institution, urinary tract instrumentation is associated with gram negative bacteremia in about 30 per cent of the patients We [illegible] that

the fibrinogen level is at the lower limits of normal, the split products were positive and the partial thromboplastin time was prolonged All of these would be consistent with the diagnosis of disseminated intra vascular coagulation and this was the diagnosis made by the hematologist who recommended treatment with heparin This is indeed a difficult problem since we have a situation in which we have made the diagnosis that the patient had had a perforation of the heart at the time of catheterization with bleeding of the peri cardium and now two days later because of diffuse intravascular coagulation hepa rin is needed to block the process This is obviously the operation of Murphy s law which states that when anything can go wrong it will but I am afraid that with this patient no matter what decision is made it will be wrong I have of course the distinct advantage over the physicians treating this patient in that I know that the presentation of this patient in this amphi theater indicates that the therapy instituted was certainly not classified as a success

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Cardio ascular r d l g t.



Fig. 1. The tricuspid leaflets show multiple recent vegetations on the valve and chordae tendineae (*arrows*).



Fig. 2. The mitral valve has minimal fibrotic and atherosclerotic changes. Note the old ruptured chorda tendinea with thickened end (*arrow*).

left main stem bronchus. On July 12, 1971, the transverse cardiac diameter was 23.75 cm., which represents an increase in silhouette size when one allows for one centimeter difference between systole and diastole. There was blunting of the left costophrenic angle, apparently by fluid.

The cardiac size in the final two films, the evening of July 12, 1971, and on the day of death on July 18, 1971, could not be evaluated, since the left heart border was obscured by considerable fluid within the left hemithorax. There was also fluid within the right hemithorax. Without the additional aid of isotope scans, ultrasonograms, or angiocardiograms it is not possible to distinguish between cardiac enlargement or pericardial effusion in accounting for the widened cardiac silhouette.

DR. KARACHORLU: At autopsy there was 2 plus edema of both legs. There was a decubitus ulcer of the right buttock measuring 10 cm. in diameter.

The right pleural cavity contained 440



Fig 3 The posterior wall of the left ventricular epicardium in the course of the po terior descending branch is d colored and roughened This area is outlined by arrows

c c and the left 370 c c of clear yellowish fluid The peritoneal cavity contained 300 c c of similar fluid The pericardial sac was extremely distended with 500 c c of fresh blood The heart was markedly en larged in situ It weighed 600 grams There was no exudate over the epicardium There was however a dark reddish brownish discolored roughened area over the poste rior wall of the left ventricle near the apex measuring 2 by 2 cm No perforation could be identified in this area The right atrium was moderately enlarged measuring 8 cm from the superior to inferior vena cava and 14 cm in circumference Its endo cardium was normal No hemorrhage or perforation of the atrial wall could be seen The orifice of the coronary sinus was en larged The fossa ovalis was 2 5 cm in diameter and closed The pectinate muscles of the atrial appendage were hypertrophied No mural thrombi were seen The tricuspid valve measured 13 5 cm in circumference (normal 12 cm) The tricuspid leaflets showed multiple ecent vegetations vary ing in size from 0 7 to 0 2 cm Some of the vegetations were located on the valve and its free edge others on the chordae tendin eae (Fig 1) No perforation of the leaflets or rupture of the chordae tendineae were noted A section from the tricuspid valve and vegetation showed acute bacterial en docarditis The vegetation contained num erous polymorphonuclear leukocytes ne crotic debris fibrin and platelets The Brown Brenn stain showed many gram positive cocci

The right ventricle was moderately en larged the inflow tract measured 10 cm and the outflow tract measured 12 cm The endocardium was intact with no hemorrhages or discolored or perforated areas The wall of the right ventricle was thick measuring 0 7 cm in the distal por tion of the pulmonary outflow tract The papillary muscles were hypertrophic and the trabeculae carneae were moderately widened The pulmonary ring measured 9 5 cm in circumference (normal 8 5 cm) The pulmonic cusps were normal The left atrium was extremely enlarged and was very thin in places It measured 7 5 cm in superoinferior diameter and 15 cm in circumference The mitral ring measured 14 cm in circumference (normal 10 cm) The leaflets of the mitral valve were mini mally fibrotic for this age with some hemo dynamic changes at their free edges There were no adhesions between the leaflets The major chorda with its 3 branches in serting into the most medial portion of the anterior leaflet was ruptured (Fig 2) This was an old rupture as judged by the thick ened rounded ends of the separated seg ments of the chorda and histologically by fibrosis and hyalinization of the ruptured ends The apical portion of the posterior papillary muscle from which the chorda arose showed considerable irregular fibrosis with streaked calcification in its tendinous portion The left ventricle was enlarged There was no aneurysm The inflow tract of the left ventricle was 9 cm and the outflow tract was 10 5 cm in length The thickness of the left ventricular wall was 1 8 cm at its base and 1 3 cm at the apex The papil lary muscles were hypertrophied The trabeculae carneae were thick and widened The endocardium of the left ventricle was normal No mural thrombus discolored area or perforation were noted The cir

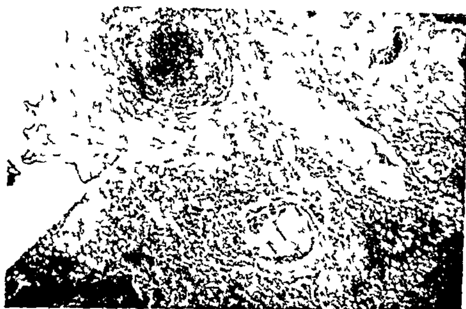


Fig 4 Section through discolored epicardium and myocardium of Fig 3 shows extensive hemorrhage and acute inflammatory process with septic thrombi in the epicardial vessels (Hematoxylin and eosin Original magnification X90)

cumference of the aortic valve was normal *measuring 7 5 cm* The cusps had the usual amount of thickening Moderate athero sclerosis was noted in the sinuses and around the orifices of the coronary arteries However the orifices of the coronary ar teries were patent the right measuring 3 mm and the left 4 mm in diameter The right coronary artery was dominant form ing the posterior descending interventricu lar branch All coronary arteries showed moderate atherosclerosis The lumen of the anterior descending branch was narrowed some 60 per cent in an area 3 cm from the origin of this vessel The posterior descend ing branch showed marked narrowing and nearly complete occlusion of its lumen 8 cm from the orifice of the right coronary artery and 7 5 cm from the apex of the heart A histologic section of the coronary artery from this segment showed marked athero sclerosis, with fresh hemorrhage into the plaque In the course of this posterior descending branch there was the discolored epicardial area described previously (Fig 3) A section through this area revealed hemorrhagic mottling extending into the midportion of the myocardium However, the corresponding endocardium was intact Several sections from this area for histo logic study showed an intense acute in flammatory process in the myocardium and epicardium (Fig 4) There were mul tiple myocardial abscesses with a poly morphonuclear exudate trailing between muscle fibers and under perivascular tis sues A considerable amount of myocardial fibrosis was present but there was no acute myocardial necrosis indicative of recent infarction The acute inflammatory process extended into the epicardium where it was associated with hemorrhage Epicardial arterial branches and veins were caught up in the inflammatory process with disruption of their walls and in instances with septic luminal thrombi Brown Brenn stains for bacteria showed gram positive cocci intra and extracellularly in the myocardial and epicardial exudate including the disrupted epicardial blood vessels Sections from the different portions of the myocardium else where failed to reveal acute inflammatory changes

The right lung weighed 650 Gm and the left weighed 450 Gm Their pleural surfaces were normal The bronchial tree was intact except for some lower lobe branches which were moderately dilated The pulmonary arteries revealed mild atherosclerotic changes There were no thrombi Some dark reddish frothy fluid could be expressed from the parenchyma There was some panlobular emphysema in the right upper lobe

The liver weighed 1,640 Gm with a dark reddish color and firmer consis c than

usual *Histologically* acute and chronic passive congestion were present *with mini* mal central and sublobular perivenous fibrosis

The first portion of the duodenum showed multiple subacute ulcers the largest 1 cm in diameter The second portion of the duodenum had a diverticulum 3 5 cm *in width* There was no gastrointestinal hemorrhage

Each kidney weighed 150 Gm The sur face was moderately *granular Histologi* cally there was vacuolization of proximal and distal tubular epithelium However, there were no acute tubular necroses The *interstitial tissues in the cortico* medullary junctional areas were infiltrated with lym phocytes and polymorphonuclears There were some hyaline and pigmented casts in Henle s loops

One parathyroid showed adenomatous hyperplasia made up largely of chief cells

The brain showed a recent hemorrhagic infarct in the right parietal lobe measuring 2 4 by 2 0 cm In addition microscopically there was an abscess in the mid brain near the *substantia nigra* Gram positive cocci were *identified in this microscopic lesion* stained by Brown Brenn The pituitary gland was normal grossly but microscopi cally there were 3 focal areas of infarction with bland appearances No bacteria could be demonstrated in these lesions

DR KRAKOWER We felt that the sudden onset of heart failure in 1956 was due to rupture of a chorda tendinea to the medial portion of the anterior leaflet of the mitral valve *Such* rupture is most frequently as sociated *with bacterial endocarditis* less so with rheumatic endocarditis infarct of the papillary muscles Marfan s syndrome or trauma to the chest None of these con ditions appears to be the underlying factor in the present case It may be assumed therefore that in the *present instance the* rupture was spontaneous This is an un common occurrence When it does occur however it is in older individuals and the chordae to the posterior leaflet of the mitral valve *are the ones* that rupture rather than those to the anterior leaflet We are inclined to believe that from 1956 onwards *the patient had* a considerable degree of mitral insufficiency with left ventricular enlargement and hypertrophy We found no evidence at the time of death of either a distinctive area of old myo cardial infarction or of a ventricular aneurysm There was myocardial fibrosis but it was patchy and particularly in the posteroinferior part of the heart supplied by the distal *portion* of the posterior de scending coronary artery We shall have occasion to refer to this area of myocardium a bit later in this discussion

We would interpret the eventful 5 days following cardiac catheterization as follows Since we were unable to find any evidence for perforation of atrial or aortic walls we believe that the *shock which occurred* dur ing cardiac catheterization was not due to hemorrhage into the pericardial sac We would ascribe it to some other mechanism We are inclined to believe that the period of shock in one or other way contributed to the renal failure although there was little anatomical evidence at the time of death of acute tubular necrosis *Much of this* failure may have been due to extrarenal factors However the necroses of the an terior pituitary and the hemorrhagic infarct of the left parietal lobe of the brain could be related to shock and Levophed therapy Aside from shock the major complication following cardiac catheterization was sep sis We would ascribe the source of the sepsis to the central venous catheter In the first place the urinary bladder was clean and while there was slight traumatic hemor rhage due to the Foley catheter there was little evidence for an acute cystitis Second blood cultures taken on 4 consecutive days following catheterization yielded positive *cultures for Staphylococcus aureus* Third the acute bacterial endocarditis involving the tricuspid valve was due to coccal and not gram negative organisms Pyemic le sions were however restricted to one small area in the mid brain and to a larger lesion *in the posteroinferior* wall of the myo cardium In this area of the myocardium *there was a diffuse suppurative and hemor* rhagic process with abscesses and with readily demonstrable coccal organisms in the lesions There was extension of the suppurative and hemorrhagic process to the overlying epicardium with involvement of the coronary arterial and venous branches In fact some of the vessels con tained colonies of *organisms* We would

ascribe the hemopericardium which we found at the time of death to seepage from these disrupted inflamed epicardial vessels. We are at a loss to explain the localization of the pyemic process to an area of myocardium, the seat of appreciable earlier myocardial scarring, except that the markedly narrowed area of the posterior descending coronary artery demonstrated a fresh hemorrhage into the atherosclerotic plaque. This additional narrowing may have favored bacterial localization by altering the pattern of the blood flow in the distal part of the artery and by the increased ischemic state of that portion of the heart.

The immediate cause of death appeared to be related in the main to sepsis and the hemopericardium. There was no anatomical evidence for disseminated intravascular thrombosis.

DIAGNOSIS. Old spontaneous rupture of chorda tendinea of mitral valve with mitral insufficiency and marked left ventricular hypertrophy and enlargement. Acute staphylococcal bacterial endocarditis of the tricuspid valve ascribable to a central venous catheter with pyemic involvement of a localized area of myocardium and epicardium, leading to disruption of walls of the epicardial vessels with resultant massive hemopericardium.

Mechanisms of cardiac arrhythmias
From hypothesis to physiologic fact

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Chicago Ill

In 1959 Drs Katz and Langendorf and I[1] pleaded for closer cooperation between experimental electrophysiologists and clinical electrocardiographers in order to verify hypothetical concepts and to attack some unresolved problems in interpreting disorders of the rhythm of the human heart Today we can state that our hopes have been surpassed far beyond our expectations Indeed the role of the two groups of investigators has been reversed Clinical applicability of results achieved in ingeniously devised animal experiments is being pointed out to an increasing extent in the writings of electrophysiologists On the other hand the clinician can now turn to experimentation on the human heart thanks to the development of harmless and precise methods permitting controlled pacing of the heart chambers the recording of action potentials from the specific conduction system and particularly the combined application of the two techniques

Among the great number of hypothetical mechanisms that have been tested in this manner twenty that are reproducible in man by cardiac pacing have been dealt with in a previous communication[2] For this presentation I selected the following seven

1 Manifestations of concealed conduction
2 Re entry pathways in the atria and/or the A V junction
3 Concealed re entry in the A V junction (atypical Wenckebach periods)
4 The question of supernormal conduction
5 Pathways for ventricular pre excitation
6 Dependence of aberrant conduction on cycle length
7 Impulse formation and Mobitz Type I block *in the ventricular conduction system*

By correlation of clinical records with their experimental counterparts some observed in our own laboratory but mostly taken from the work of other investigators I shall try to demonstrate how well or how poorly our conjectures have stood up to experimental testing I shall mention some remaining areas of controversy and shall also include speculations awaiting experimental verification in the future

Manifestations of concealed conduction

Fig 1 (A) is a reproduction of part of a record published by Simon and Langen

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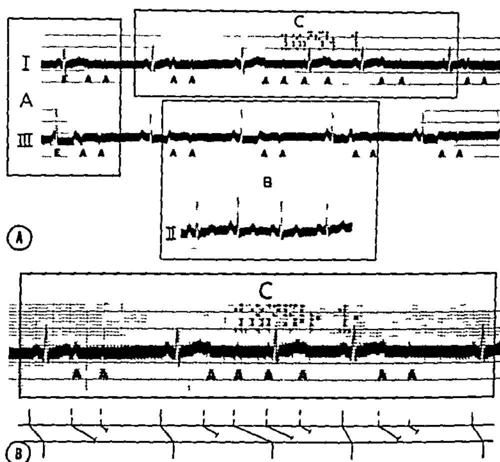


Fig 1 (A) Sinus rhythm with repetitive nonconducted atrial premature ectopic beats Frames A and B are discussed in text Frame C (with diagram) is reproduced in (B) showing repetitive nonconduction of atrial premature beats due to concealed A V conduction The length of the oblique lines in the diagram indicates the extent of penetration of the A V junction by ectopic atrial impulses (Fig 1 A is reproduced from Katz L N and Pick A Clinical Electrocardiography Part I The Arrhythmias Philadelphia 1956 Lea & Febiger Reproduced with permission)

dorf[3] in 1949 Leads I and III show repetitive nonconducted atrial premature systoles each labelled A while in Lead II the sinus rhythm is undisturbed Three different points of interest are framed and labelled A B and C Frame A shows a fixed coupling of 0 32 sec of the second premature beat to the first On this basis a re entry mechanism in the atria was assumed This possibility was documented experimentally by Han and associates [4] who proved that the sinus node was included in the re entry path However this does not seem to apply to our clinical case In Frame B it can be seen that the sinus interval of 1 66 sec including the two premature P waves, equals two undisturbed sinus cycles in other words that the ectopic atrial impulse is interpolated That an ectopic atrial impulse capable of producing an atrial echo may or may not enter the sinus node and reset its cycle has been demonstrated in man experimentally by Goldreyer and Damato [5] In our clinical case the entrance block of the premature impulse is bidirectional toward the sinus as well as toward the A V junction

However the antegrade block is not always complete as shown in Frame C reproduced with a diagram in Fig 1 (B) In the latter failure of the ventricles to respond to the second of a pair of premature atrial impulses is attributed to concealed penetration of the A V junction by the first of the pair Yet this takes place to a varying extent With less deep penetration of the first premature atrial impulse—in the middle of the record—the subsequent ectopic impulse can reach the ventricles only with great delay

We were able to reproduce this at a much later time in another patient by atrial pacing as illustrated in Fig 2 [6] When an extra impulse X was interposed into a

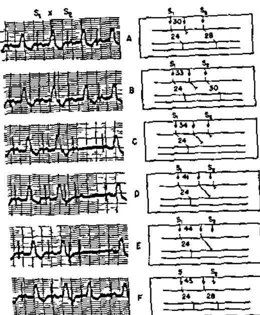


Fig 2 Concealed A V conduction in paired artificial atrial pacing *S* Basic driving stimuli *X* interpolated extrastimuli numbers sec /100 (Fig 2 is reproduced from Langendorf R Pick A Edelist A and Katz L N Experimental demonstration of concealed A V conduction in the human heart Circulation 32 386 1965 Reproduced by permission of the American Heart Association Inc)

stimulation cycle progressive lengthening of the interval S_1 X determined the depth of its concealed conduction and thereby the success or failure of conduction of S_2

In the same case atrial pacing was used to reproduce in man the classical experiment carried out in 1925 by Lewis and Master[7] on concealed A V conduction in dogs A comparable result was observed in our experiment in human subjects (Fig 3)[8] A 2 1 ventricular response with a P R of 0 28 with rapid atrial pacing changed to a 1 1 response with a shorter P R of 0 24 when the pacing rate was one half The assumption is that the longer P R is the aftereffect of concealed conduction into the A V node of the apparently blocked stimulus We could verify this interpretation by repeating such an experiment with a His bundle recording (Fig 4) In Panel *B* during rapid pacing of the atria alternate impulses (*S*) are not followed by a His deflection while the A H interval of conducted impulses measures 140 msec Thus there is a 2 1 block proximal to *H* presumably in the A V node At half the stimulation rate in Panel *C* there is a ventricular response to each stimulus with the A H interval reduced to 110 msec This is similar to that of the control Panel *A* obtained during sinus rhythm at a rate of 70

Perhaps the most convincing documentation of the concealment of an impulse within the A V junction was recently provided in the case of so-called pseudo A V block (Fig 5) A clinical instance the second in our material since the original description by Langendorf and Mehlman[9] 25 years ago shows in Lead II sudden prolongation followed by failure of conduction in a regular sinus rhythm As indicated in the diagram this is attributed to aftereffects of two premature A V junctional discharges blocked in both directions This interpretation is supported by Lead III, where the interpolated junctional discharge is conducted to the ventricles with aberration Documentation of such a spontaneously occurring mechanism was provided by Rosen and associates[10] in a clinical case using His bundle recordings and experimentally by Moore and associates[11] in the rabbit heart recorded through a microelectrode impaled into the A V junction

Re entry pathways in atria and/or A V junction

The combination in man of cardiac pacing and His bundle recordings[12-14] has made it possible to confirm a number of deductive and empirical interpretations of standard clinical records that have important prognostic and therapeutic implications For example Mobitz Type I A V block can be distinguished from Type II the location of the block in the conduction system can be ascertained and combinations of block can be recognized[15-26] Likewise continued reciprocal beating of atria and ventricles has been identified as the cause of many—although not all—supraventricular paroxysmal tachycardias[27-29] Leaning on convincing clinical experimental data[30-35] we are able to understand the spontaneous initiation and termination of paroxysms in physiologic terms One such instance is illustrated in Fig 6 In the upper strip a junctional circus movement can be postulated to be interrupted when a spontaneous

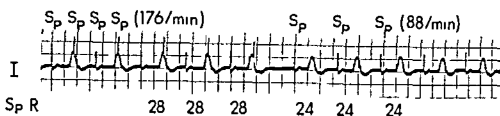


Fig 3 Concealed A V conduction in rapid atrial pacing *Sp* Atrial response to pacer stimulus (Fig 3 is reproduced from Langendorf R Pick A Edelist A and Katz L N Experimental demonstration of concealed A V conduction in the human heart Circulation 32 386 1965 Reproduced by permission of the American Heart Association Inc)

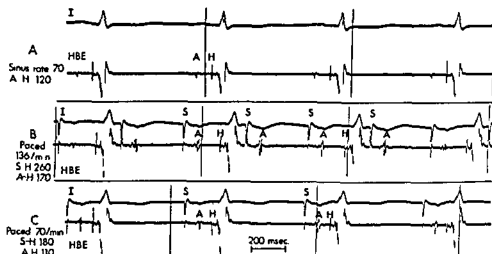


Fig 4 Concealed A V conduction demonstrated by His bundle recording during rapid atrial pacing (*B*) Panel *A* Control before pacing *S* Stimulus artifact in His bundle electrogram (HBE) *A* atrial potential *H* His potential *A H* transnodal conduction time (approximate)

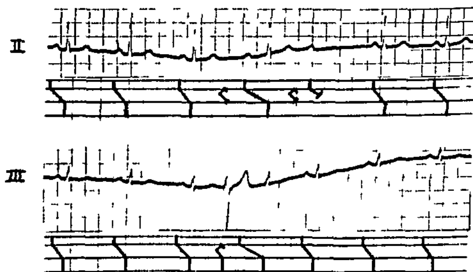


Fig 5 First degree and Type I second degree A V block imitated by blocked A V junctional premature beats

premature atrial discharge at the upper arrow, invades and blocks the circus path it is resumed in the lower strip when a similar spontaneous atrial ectopic impulse at the lower arrow, conducted with delay to the ventricles initiates repetitive alternating echoes of atria and ventricles We also learned why in Type I A V block paroxysms of reciprocating tachycardia prevent the completion of a Wenckebach period once a critically prolonged P R is reached (Fig 7) it sets the stage for the first as well as consecutive re entry processes in the A V junction[26,27] Another

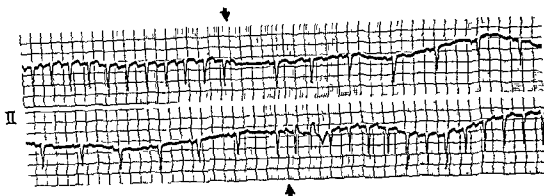


Fig 6 Termination (↓) and resumption (↑) of reciprocating supraventricular paroxysmal tachycardia by atrial premature beats The right bundle branch block contour of the first and second beat of the recurrent tachycardia is due to aberrant ventricular conduction

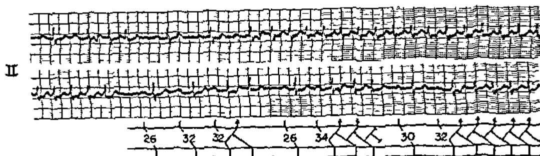


Fig 7 Repetitive reciprocating supraventricular tachycardia initiated by critical (0 32 to 0 34 sec) P R prolongation in Type I second degree A V block (caused by digitalis)

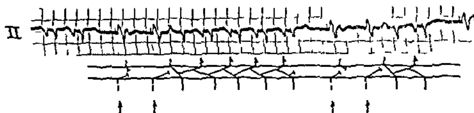


Fig 8 Intermittent reciprocating supraventricular tachycardia initiated by prolonged A V conduction time of ventricular captures during A V dissociation resulting from ventricular pacing

more rare example of the crucial role of slowed A V *conduction in the initiation* and perpetuation of atrial and ventricular echoes is shown in Fig 8 During demand pacing of the ventricles indicated by the pairs of upright arrows A V dissociation is replaced *transiently by* atrioventricular reciprocation *subsequent to the prolonged* P R interval of a ventricular capture by a sinus impulse[33]

However not all known *varieties of* junctional tachycardia have an experimental counterpart Continued reciprocation remains to be proved in cases with a *bidirectional exit block*[39] Fig 9 shows an example with two diagrams which may or may not require amendment In a junctional tachycardia there is repetitive group beating of the ventricles and atria corresponding to a 5 4 antegrade and a 5 3 *retrograde* Type I block In the left diagram a continuous regular junctional discharge is assumed and double block in retrograde direction attributed to concealed backward penetration of each fourth junctional impulse In the right diagram

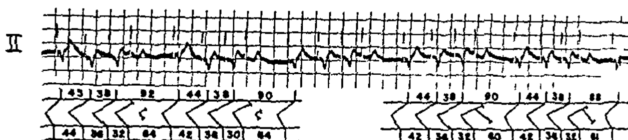


Fig 9 A V junctional tachycardia with Wenckebach periods of forward and retrograde conduction For explanation of the two diagrams see text

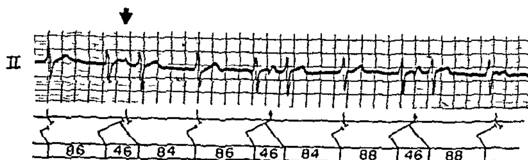


Fig 10 Subatrial re entry in A V junctional rhythm with reciprocal beating

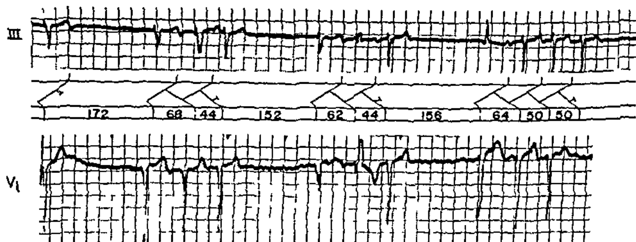


Fig 11 Subatrial re entry in A V junctional rhythm during atrial fibrillation (A V dissociation) in Lead V1

concealed subatrial antegrade re entry is assumed, initiated by the prolonged concealed retrograde conduction which resets the cycle of the junctional focus

Be that as it may such not too rare cases have a bearing on the unsettled dispute[40 43] as to whether or not the atria are a necessary link for reciprocal beating of the ventricles or to put it in physiologic terms whether functionally dissociated pathways converge to a common path not only in the distal but also in the proximal A V junction

Other records lead us to believe that in ventricular echoes the reversal of the retrograde impulse takes place at a subatrial level For instance in Fig 10 showing a case of reciprocal beating at the arrow a sinus P wave is sandwiched between the first couple in contrast to clearly retrograde P waves in the second and third couple Perhaps less convincing but plausible is our interpretation of Fig 11 Similar groups of two or three fast beats follow junctional escapes In Lead III the retrograde P waves identify the arrhythmia as reciprocal

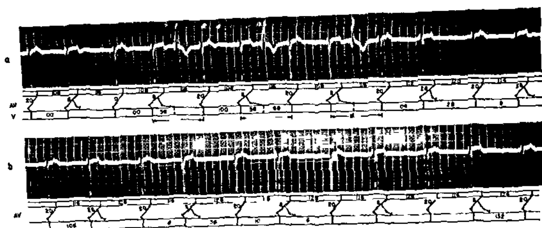


Fig 12 Concealed (blocked) reciprocal beating in A V junctional rhythm with delayed retrograde conduction Note that in *b* the longer R P interval of 0 28 is always followed by prolongation of the manifest junctional cycle from 1 08 to 1 36 sec

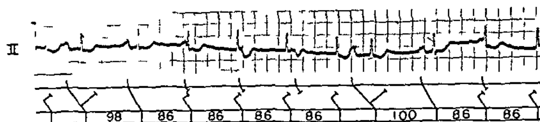


Fig 13 Concealed retrograde re entry (attempt at atrial echo) in incomplete A V dissociation which developed after acceleration of A V junctional impulse formation by digitalis

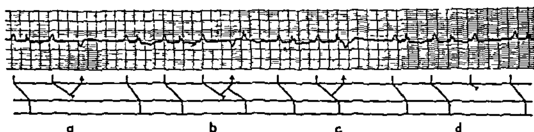


Fig 14 Second-degree A V block (Type I) with concealed A V conduction with three atrial echoes and one ventricular echo

beating In Lead V_1 on the next day when atrial fibrillation had developed and the atria became unresponsive the assumed reciprocal path would have to be below the atrionodal junction [44]

Concealed re entry in A V junction

Reciprocal beating is one of the manifestations in the human heart of the experimentally proved existence of at least two A V tran mission systems having different functional properties [37 40] These potential re-entry pathways may not be utilized to their entire length and the circus movement may be incomplete Thus in 1950[45] we explained a curious case (Fig 12) of slow junctional rhythm in which R P intervals and junctional cycles alternated concomitantly by concealed antegrade re entry postponing the next junctional discharge The clue was found in the upper record of another day which showed that the prolongation of the ventricular interval to 124 was the result of junctional re-entry actually completed in the middle but concealed at both ends of the record By the

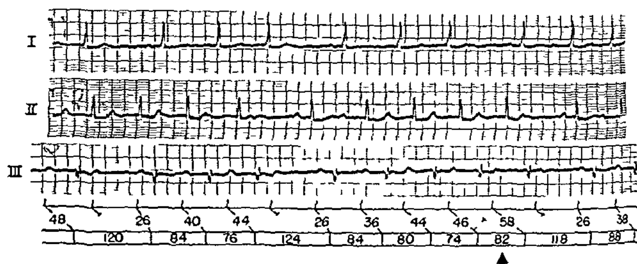


Fig 15 Concealed re entry in the A V junction (attempt at atrial echo) causing an atypical Wenckebach period

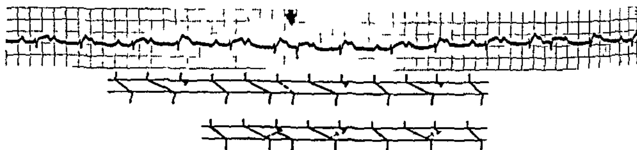


Fig 16 Atypical Wenckebach periods due to a double A V path (upper diagram) or concealed retrograde followed by manifest antegrade re entry (lower diagram) in the A V junction

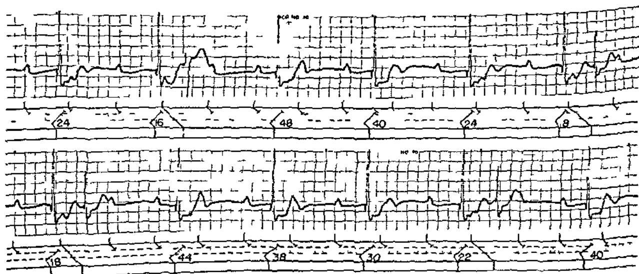


Fig 17 Incomplete A V dissociation due to advanced unidirectional A V block Concealed retrograde conduction of idioventricular impulses permits ventricular capture by sinus impulses (with aberrant ventricular conduction) only during a supernormal phase of A V conduction

same token in another case (Fig 13) with incomplete A V dissociation we explained the failure of a junctional escape to occur at the expected time of 86 by a concealed retrograde re entry attempt induced by prolonged antegrade conduction of early ventricular captures[46] Experimental data now available in the literature[15 47] allow us to interpret with confidence other variants of such mechanisms example,

II
S 60/MIN
II
P
S 136/MIN
III
P P P P P P P
S 150/MIN
III
P P P P P P

Fig *18* Unidirectional A V block in Stokes Adams syndrome The first strip shows a period of prolonged ventricular asystole followed by two ectopic ventricular beats before A V conduction is resumed Note constancy of P R in conducted beats (Type II antegrade A V block) In the second strip such intermittent periods of asystole are prevented by responses to transvenous ventricular asynchronous pacing at a rate (*S*) of 60 Pacer impulses falling at long distances after a P wave were conducted *backwards to the atria* (*P*) *When the* pacing rate was increased to 136 (third strip) each artificial impulse reached the atria at a constant R P interval of 0 24 sec Thus the A V block was proved to be unidirectional With further acceleration of the pacing rate to 150 the atria respond at a 3 2 ratio with a Wenckebach phenomenon the second R P lengthening to 0 26 sec This region of Type I retrograde block was probably proximal to the Type II antegrade block [8]



Fig *19* Sudden protracted ventricular arrest in Type II second degree A V block A V conduction is resumed following spontaneous escape of a subsidiary ectopic pacemaker

some atypical features of atrioventricular Wenckebach periods [48]

An unusual case is illustrated in Fig 14 in which four different events are labelled *a* to *d* for presentation Part *d* shows a simple 3 2 Wenckebach period In *a* to *c* the sequence of regular sinus impulses is disturbed by atrial echoes induced by greater delay in antegrade conduction These echoes occur regardless of whether the initiating sinus impulse reaches the ventricles as in *c* or fails to do so as in *a* and *b* However when it fails the unused portion of the antegrade path provides a potential avenue for a ventricular echo a sweep that is actually completed in portion *b*

In the Wenckebach periods shown in Fig 15 the arrow indicates that against the rule the increment of P R is largest before the dropped beat Previously [49] we tried to explain this observation by assuming a critical state of A V conductivity before its total failure Today we can attribute it to the aftereffect of an attempted re entry via a retrograde path that has opened up after sufficient delay of antegrade conduction as indicated in the diagram Fig 16 illustrates an opposite event In the middle of a Wenckebach period at the arrow the P R unexpectedly shortens before the period is resumed and completed Originally [50] we thought that this might be

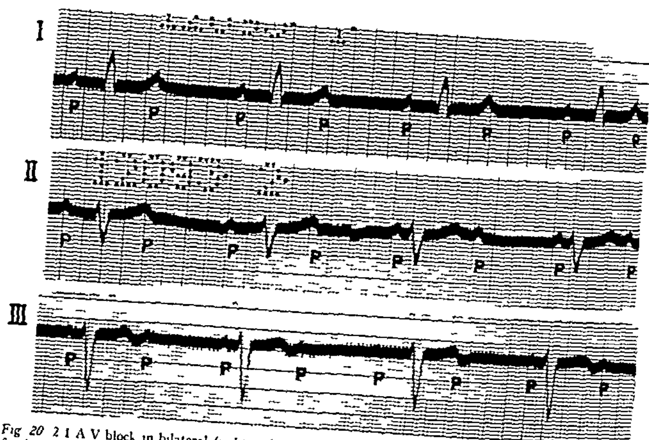


Fig 20 2 1 A V block in bilateral (right and left anterior fascicular) bundle branch system block Note two fixed ranges (0 16 and 0 34 sec) of P R intervals in the conducted beats

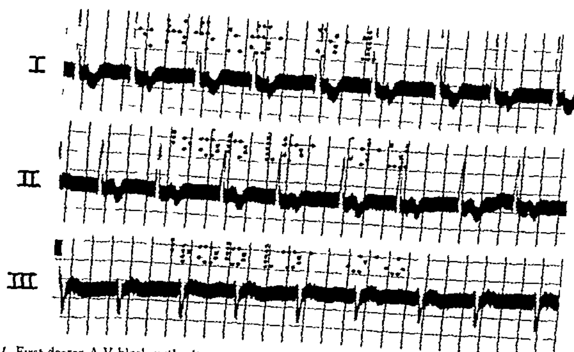


Fig 21 First degree A V block with alternation of P R intervals (causing ventricular bigeminy) For interpretation see text and Fig 22

due to supernormal conduction through depressed A V junctional tissues In the light of advanced knowledge other interpretations appear more likely In the upper diagram two longitudinally dissociated conduction pathways with different conduction speeds are considered The lower diagram indicates that the premature QRS is unrelated to the P wave preceding it Rather it is a ventricular echo reflected from an abortive (concealed) attempt at an atrial echo If true this interpretation

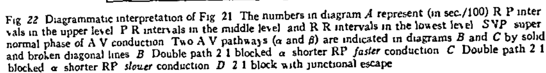


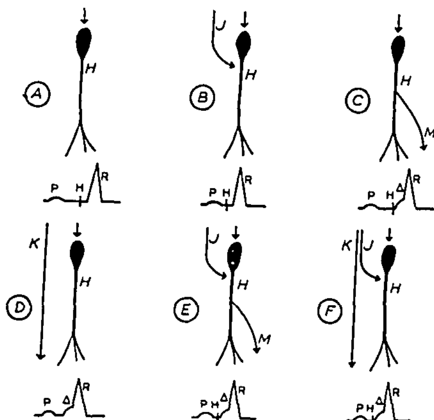
Fig 22 Diagrammatic interpretation of Fig 21 The numbers in diagram *A* represent (in sec./100) R P intervals in the upper level P R intervals in the middle level and R R intervals in the lowest level *SVP* supernormal phase of A V conduction Two A V pathways (α and β) are indicated in diagrams *B* and *C* by solid and broken diagonal lines *B* Double path 2 1 blocked α shorter RP *faster* conduction *C* Double path 2 1 blocked α shorter RP *slower* conduction *D* 2 1 block with junctional escape

serves as evidence against inclusion of the atria into the re entry path in reciprocal beating (see above)

Supernormal conduction

The concept of supernormal A V conduction is hypothetical and indeed was severely criticized by Moe and his associates [51] It is unlikely in the case of unexpected shortening of conduction time of successive impulses traveling in the *same* direction [52 53] However we still consider the mechanism of supernormal conduction in advanced A V block (Fig 17) when captures occur exclusively and predictably during a narrow limited period early in the ventricular cycle In the example shown the range for A V conduction expressed in R P intervals is 0 16 to 0 22 sec We attribute this to backward penetration of ventricular impulses transiently converting a region of unidirectional conduction into one of supernormal conduction [50] We were able to reproduce this at will in a number of cases of advanced A V block requiring ventricular pacing during slow pacing rates and to prove the existence of unidirectional block by driving the ventricles faster than the spontaneous rate of the sinus node (Fig

Fig 23 Schematic representation of pathways for A V conduction in ventricular pre excitation *1* Total A V bypass *2* normal path through A V node and bundle of His *3* partial A V bypass (Fig *23* is reproduced from Katz L N and Pick A Clinical Electrocardiography Part I The Arrhythmias Philadelphia 1956 Lea & Febiger Reproduced with permission)



Diverses combinaisons possibles des voies de pre-excitation
a) Conduction auriculo ventriculaire normale
b) Syndrome du P R court sans onde delta (Fibres de James)
c) Syndrome de W P W avec espace P R normal (Fibres de Mahaim)
d) Syndrome de W P W avec P R court et espace P H normal par voie de pre excitation auriculo ventriculaire directe (Faisceau de Kent)
e) Syndrome de W P W avec P R court et P H court par association de fibres de James et de fibres d Mahaim
f) Syndrome de W P W avec P R court et P H court par association d un faisceau de Kent et de fibres de James
(Abreviations H = faisceau de His J = fibres de James M = fibres de Mahaim K = faisceau de Kent)
Pour la discussion voir le texte

Fig 27 A schematic correlation of the manifestations in the electrocardiogram of the function of various total and partial A V bypasses *J* James fibers *K* Kent fibers *M* Mahaim fibers *H* His bundle potential and its temporal relation to P and R waves with normal A V conduction (*A*) and in variants of ventricular pre excitation (*B F*) see text (Fig 1 in Coumel and associates[66] reproduced with permission from Coumel Waynberger Slama and Bouvrain Acta Cardiol 26 188 1971)

bundle branch block (Fig 28) we attributed persistence of the latter to a bypass pre exciting the contralateral left ventricle [67] But this assumption was untenable in another case (Fig 29) of intermittent right bundle branch block associated with pre excitation of Type B In the framed Lead V_1 a deep negative delta wave is followed by a large late R wave Here right sided pre excitation did not preclude the bundle branch block in the ipsilateral ventricle Pending a better explanation based on anatomic and physiologic study of such cases, we propose that a complete right sided A V bypass could insert proximal to the region of block in the right ventricular conduction system

Dependence of aberrant conduction on cycle length

Turning now to some other problems of abnormal intraventricular conduction we will consider causes of aberrant conduction of escape beats An example is shown in Fig 30 In a digitalized patient with atrial fibrillation regular escape beats the smaller QRS complexes in each lead show a higher degree of right bundle branch block than the ones conducted faster The

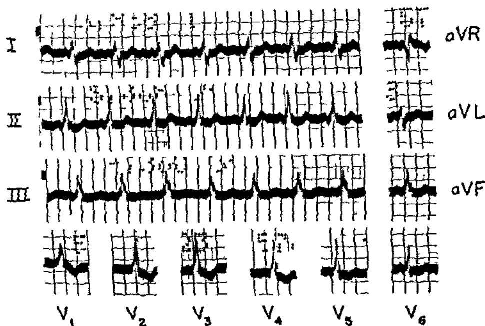


Fig. 28. Ventricular pre-excitation Type A in the presence of a right bundle branch block.

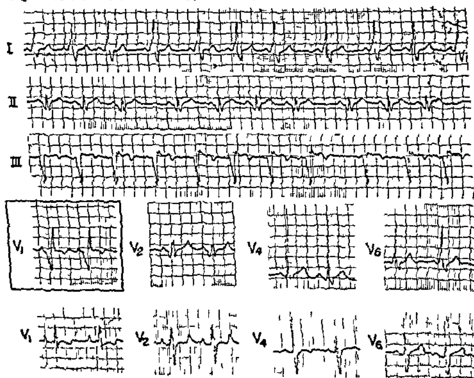
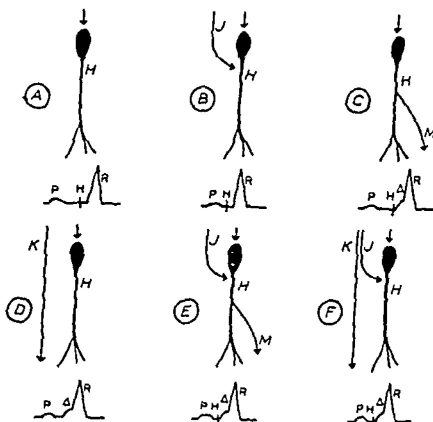


Fig. 29. Intermittent ventricular pre-excitation Type B in the presence of right bundle branch block. Pre-excitation is seen in the limb leads and upper series of chest leads and has disappeared in the lower series of Leads V_1 to V_6.



Diverses combinaisons possibles des voies de pré-excitation
a) Conduction auriculo-*ventriculaire normale*
b) Syndrome du P R court sans onde delta (*Fibres de James*)
c) *Syndrome* de W P W avec espace P R normal (Fibres de Mahaim)
d) Syndrome de W P W avec P R court et espace P H normal par voie de *pré-excitation* auriculo-ventriculaire directe (Faisceau de Kent)
e) *Syndrome* de W P W avec P R court et P H court, par association de fibres de James et de fibres de Mahaim
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Dependence of aberrant conduction on cycle length

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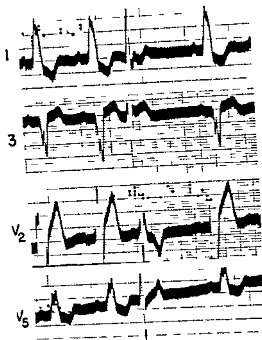


Fig 33 Left bundle branch block (QRS 0 16 sec) with premature beats of bilateral (right and left anterior fascicular) bundle branch block configuration having less QRS prolongation (0 14 sec)

six explanations that have been offered for this apparent paradox are listed in Table I The first and the last three of the listed mechanisms are purely hypothetical and may apply only exceptionally The effects of phase 4 depolarization have been determined by Singer and co workers[76] who have performed microelectrode studies of automatic Purkinje cells Aberration of R S T depends on the magnitude of the transmembrane potential at the time of an ectopic impulse This take-off potential may be reduced as a result of (1) incomplete repolarization in the case of a premature impulse or (2) diastolic phase 4 depolarization with a late impulse The latter mechanism is most likely in cases such as that illustrated in Fig 31 Normal intraventricular conduction is maintained up to a cycle length of 112 is slightly aberrant with a cycle of 116 and totally aberrant with cycles equal to or longer than 120 In other cases Rosenbaum s[71] concept of fascicular origin of ectopic beats can be more readily applied In a case of atrial fibrillation (Fig 32) escape beats can be identified in the routine electrocardiogram on top by their constant long cycle, as well as by the pattern of a posterior fascicular block Their ventricular origin presumably in the left anterior fascicle could be documented by the His electrogram They lack an H deflection that precedes the conducted beats and the fusion beat (*F*) at a normal H V interval (lowest panel)

However the possibility of supernormal conduction in depressed bundle branches cannot be entirely dismissed one pertinent example is shown in Fig 33 In a case of left bundle branch block premature beats have a typical contour of a bifascicular right and left anterior conduction defect Conceivably the ectopic beats could arise in the posterior fascicle of the left bundle branch system distal to a region of high predivisional unidirectional block However it could also be postulated that supernormal conduction through the main left bundle unmasks a latent block in the right bundle branch system and left anterior fascicle[77]

Impulse formation and Mobitz Type I block in ventricular conduction system

One more aspect of abnormal intraventricular conduction will highlight how new techniques have borne out hypotheses (Fig 34) In a case of intermittent ventricular bigeminy after progressive lengthening of the coupling interval of ventricular premature beats from 54 to 70 we speculated on an intraventricular Wenckebach mechanism[78] located either in a re entry path or at the Purkinje myocardial junction Support for this assumption was found in a patient with pacemaker dysfunction (Fig 35) Progressively longer stimulus to response intervals preceded a nonresponse The prolonged latency after two successive failures as seen at the end of the record could be attributed to decremental propagation of the pacer stimulus

That a Wenckebach type of block can indeed occur between contractile myocardium and Purkinje fibers was demonstrated in 1961 by Alanis and associates[79] in Mexico in the rapidly driven dog heart Recently Greenspan and associates[80] demonstrated this in hypoxic canine Purkinje fibers as well as in excised human ventricular tissue

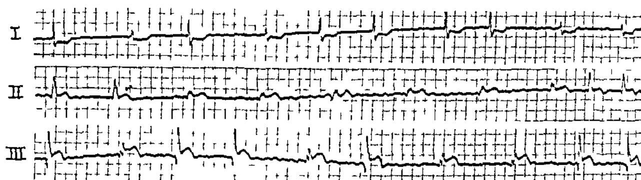


Fig 30 Atrial fibrillation with slow ventricular response and A V junctional escapes with aberrant ventricular conduction (smaller QRS complexes in each lead) causing temporary A V dissociation in the middle of Lead II

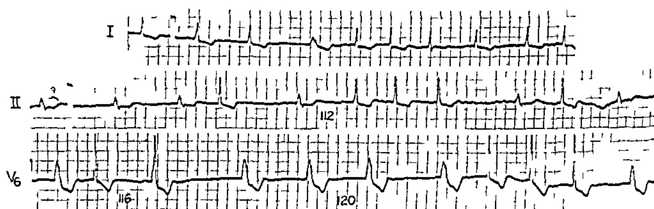


Fig 31 Intermittent (bradycardia dependent) left bundle branch block in atrial fibrillation and left ventricular hypertrophy The degree of the intraventricular conduction disturbance is determined by the cycle length

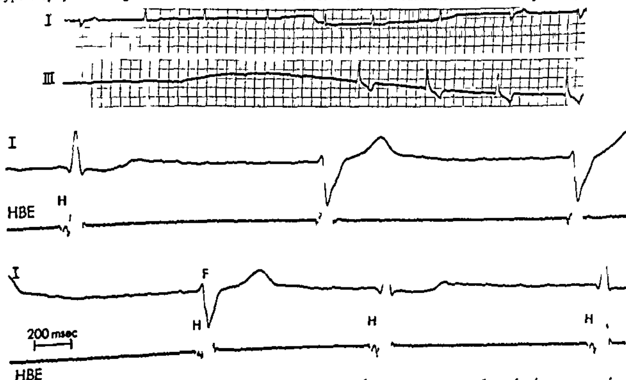


Fig 32 Atrial fibrillation with a slow ventricular response and repetitive escape of a subsidiary pacemaker probably located in the anterior fascicle of the left bundle branch His bundle recording (HBE) reveals that *H* potentials precede only conducted beats and a fusion beat (*F*)

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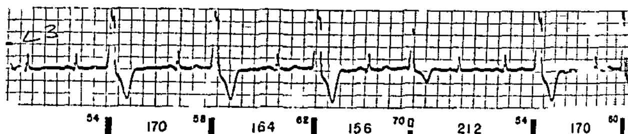


Fig 34 Intermittent ventricular bigeminy Progressive prolongation of coupling interval (upper small numbers) of ventricular premature beats The longest coupling (0 70 sec) before intermission approaches the length of the sinus cycle resulting in a ventricular fusion beat (interrupted white black bar in the diagram) Note that the irregular interectopic intervals (lower larger numbers) have the structure of a Wenckebach period



Fig 35 Type I exit block of impul es of a failing artificial ventricular pacemaker In the diagram the dots indicate pacer discharge horizontal lines indicate the duration of latency of ventricular responses (↓) Interrupted horizontal lines indicate decremental (concealed) conduction from point of stimulation into surrounding myocardium (Courtesy of Dr Sidney Goldstein Rochester N Y)

Table I Potential mechanisms of aberration of escape beats

1 Preferential A V path (origin in Mahaim fibers)[68 69]
2 Phase 4 depolarization[70]
3 Ventricular (fascicular) origin[71]
4 Functional dissociation within a bundle branch[72]
5 Wedensky facilitation[73]
6 Supernormality of intraventricular conduction[74 76]

perfused by potassium in a high concentration

Conclusion and summary

A correlation of deductive interpretations of various disorders of the cardiac rhythm encountered in clinical electrocardiography with mechanisms established in animal and man by the use of modern techniques of registration confirms many but not all previously made assumptions The present correlation deals with only certain selected mechanisms amenable to experimental testing at the time of preparation of the presentation, in the spring of 1972 In the meantime rapid progress in electrophysiologic techniques has enlarged the possibilities of correlation of clinical presumptions with physiologically established facts Thus the impact of detection of 'gating' mechanisms operating within the atrioventricular and intraventricular conduction system[81] and the role of slow conduction studied in a new preparation in the genesis of ventricular arrhythmias caused by re entry[82 83] and/or parasystolic activity—with and without exit block[84 90]—will be included in a future more extensive review article

The author wishes to thank Drs D Durrer and H J J Wellens in Amsterdam and Dr P Coumel and associates in Paris for their kind permission to reproduce Figs 26 and 27 and Dr S Goldstein in Rochester N Y for use of his observation in Fig 35

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Drug therapy of heart disease in pediatric patients

II The treatment of congestive heart failure in infants and children with digitalis preparations

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In general when drugs are administered to young pediatric patients the dosage regimen must be adjusted to take into account the immaturity of the various systems that control the amount of drug in the body at any time Thus the usual rule is that infants require smaller doses than do older children and adults However clinical experience has demonstrated that pediatric patients in congestive heart failure require higher doses of digitalis glycosides per unit weight than do adults

The glycoside most commonly used to treat pediatric patients is digoxin Its advantages are that it is readily absorbed is available in convenient dosage forms and is rapidly excreted from the body In this paper we will summarize the data currently available concerning the factors which control the proper dosages of digoxin in infants and children and discuss the possible explanations for this seemingly paradoxical situation of higher digitalis requirement per unit weight in infants

The pharmacokinetics of digitalis glycosides could not be studied until recently, due to the difficulty of measuring them in biological fluids Thus we are only now beginning to determine whether the apparent need for higher doses of digitalis in infants is due to poorer absorption to more rapid excretion or to greater end organ resistance

Pharmacokinetics of digoxin

Absorption It is apparent from a study of the published data concerning the absorption of digoxin in infancy that there is little difference if any between the ability of pediatric patients to absorb this glycoside and for adults to absorb it When serum levels of digoxin were studied by the radio immunoassay technique it was apparent that infants receiving maintenance therapy orally were absorbing the drug as well as adults [1-5] Furthermore in 20 infants aged 6 days through 5½ months maximum blood levels of digoxin were achieved within 30 minutes after intramuscular administration and in 1 to 3 hours after oral adminis

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tration[6] This study was conducted by administering varying amounts of tritiated digoxin to patients in single doses[6]

Distribution The pharmacology of the digitalis glycosides has been studied extensively in adults through the use of tritiated digoxin[7] There was a constant relationship in mature individuals between tissue and serum digoxin concentrations with a ratio of 30 to 1 between the myocardium and the serum In these studies the digoxin concentration was determined at a variable time after the administration of a single dose of digoxin In a similar study 9 infants were given a single intravenous dose of digoxin and the tissue concentrations were measured after a variable amount of time had passed The levels in these infants were claimed to be similar to those seen in adults[8,9] although the actual value reported for adults is 52 ng per gram wet weight of heart[10] while the value reported for one 3 month old infant was 5 6 ng per gram wet weight of heart[8]

In another study patients who were being maintained on digoxin therapy were evaluated with tritiated digoxin and similar values were reported for infants and adults The concentration of digoxin per gram wet weight of heart reported by these investigators varied between 150 and 190 ng[9]

The data which are available currently do not shed light upon the question of whether or not tissue digoxin concentration must be higher within the heart muscle for therapeutic effect in infants than in adults However they imply that there can be a wide difference between the tissue concentration achieved after a single intravenous dose and that achieved after prolonged maintenance therapy On the other hand it appears that the time required for distribution of a dose of digoxin is approximately the same in infants as in adults *Studies of the first phase of disappearance* of digoxin from the circulation in patients of all ages indicate that the half time for distribution is between 0 5 and 1 5 hours[4,6]

Excretion The mean half time for disappearance of a single dose of digoxin after this first phase (distribution) is approximately 34 hours in the adult (range 17 to 65 hours)[7] In studies of a series of infants and young children the mean half time for disappearance of digoxin (after distribution) was found to be 32 5 hours (range 18 to 48 hours)[8] These data are supported by the observation that 62 2 per cent of a dose of tritiated digoxin was *recovered in* the urine of adult patients within 3 days after administration[7] and 55 per cent of a dose was recovered in a 3 day collection of urine from infants[8]

In one study 5 infants with evidence of abnormal renal function (BUN elevations and abnormal inulin clearance) were included The mean half time for elimination of digoxin in this group of patients was 50 hours (range *36 to 96* hours) and only 32 per cent of the dose was recovered in the urine after a 3 day collection[6] These data support the previous findings that patients with impaired renal function excrete digoxin more slowly than normals and should have their dose adjusted downward to prevent the build up of excessive serum and tissue concentrations[7,11]

Mechanism of action

Most experimental studies on the mechanism of action of the cardiac glycosides have been conducted with ouabain It is generally assumed that the results would be similar if digoxin were used

There is no experimental evidence that suggests that the digitalis glycosides have a direct effect on myocardial contractile proteins It is also apparent that the glycosides do not strengthen *contractile force by in*fluencing myocardial energy metabolism

The glycosides probably act by facilitating the transmission of cell *membrane* excitation to the contractile elements *within* the cell[12] It is thought that this *effect is* related to a specific inhibitory effect of the *drug on the* Na^+-K^+ activated adenosine triphosphatase (Na-K ATPase) in the *membrane This inhibition* probably leads indirectly to an increase in the free Ca^{++} *concentration* within the myocardial cell This change in Ca^{++} concentration is thought to be the immediate trigger for the contractile process[12]

Several investigators have studied the possibility that ouabain may effect myo*cardial* Na-K ATPase differently at different ages There was no age related difference in the Na-K ATPase activity of tissues from the hearts of 7 newborn lambs and 7 adult sheep Furthermore there was

Table I. Digoxin serum levels in infants and children on maintenance therapy

Reference	*Age*	*Mean digoxin dose (mg./kg.) per 24 hrs.*	*Mean digoxin serum level (ng./ml.)*
5	3-30 days	0.018	1.8
2, 3	1-11 mos.	0.021	2.7
5	1-12 mos.	0.017	2.1
2, 3	2-14 yrs.	0.015	1.4
1	2-5 yrs.	0.016	1.4
1	> 5 yrs.	0.009	0.9

Table II. Relationship between digoxin dose, weight, surface area, and digoxin serum level in infants, children, and adults

Reference	*Age*	*Mean digoxin dose per 24 hrs.*		*A*†	*B*‡
		*mg./kg.**	*mg./M.²**		
5	3-30 days	0.018	0.35	1.7//1.5	3.3//1.5
2, 3	1-11 mos.	0.021	0.36	1.8//2.0	3.9//2.0
5	1-12 mos.	0.017	0.33	1.6//1.6	3.1//1.6
2, 3	2-14 yrs.	0.015	0.4	2.0//1.07	2.7//1.07
1	2-5 yrs.	0.016	0.4	2.0//1.07	3.0//1.07
1	> 5 yrs.	0.009	0.27	1.3//0.7	1.6//0.7

*Values for average weight and surface area for the respective age group were assumed where not given in the references.

†$\frac{\text{mg./M.}^2 \text{ infant}}{\text{mg./M.}^2 \text{ adult}} // \frac{\text{ng./ml. infant}}{\text{ng./ml. adult}}$

‡$\frac{\text{mg./kg. infant}}{\text{mg./kg. adult}} // \frac{\text{ng./ml. infant}}{\text{ng./ml. adult}}$

no difference in ouabain binding activity or in the stability of the binding complex between the tissues from lambs and those from sheep.[13] On the other hand, median myocardial Na-K ATPase activity was significantly greater in fetal and newborn puppies than in mature dogs.[14] If these latter results are confirmed, they may provide a partial explanation for the need of higher digoxin doses in infancy since they indicate that more drug may be needed to effect the same alteration in intracellular Ca^{++} concentration in the immature myocardium.

Dosage recommendation

1. *Neonatal period.* Newborn infants are more sensitive to digitalis than are older infants. Thirty-three per cent of 80 healthy newly born premature infants showed signs of digitalis intoxication when they were treated with digoxin, 0.075 mg. per kilogram of body weight.[15] Only 9 per cent developed toxic signs when the dose was reduced to 0.050 mg. per kilogram of body weight. Similarly, bradycardia and atrioventricular block occur with greater frequency in newly born full-term infants than in 2- to 4-month-old infants given similar doses per unit of body weight.[16] Therefore, all neonates should be given lower doses per unit of body weight than 1- to 12-month-old infants.

2. *Infancy.* Several investigations have been conducted to examine the relationship of digitalizing and maintenance doses to

Table III. Digoxin dosage in infants and children—mg./kg.

Route of administration	*Newborn infant*	*Infants up to 1 yr.*	*1 to 2 years*	*Over 2 years*	*Maintenance dosage*
Intramuscularly, orally	0.05	0.07	0.06	0.04 to 0.05	20 to 30% of TDD
Intravenously	75% of above	75% of above	75% of above	75% of above	

Additional data: 1. 50 to [illegible]0 per cent of the TDD are given stat, the remainder in 2 doses at 6 to 8 hour intervals.
2. Digoxin is available in special form for pediatric use: parenteral digoxin 0.1 mg. = 1 c.c. (adult form 0.25 mg. = 1 c.c.); oral digoxin 0.05 mg. = 1 c.c.

serum concentration. They are summarized in Table I. Two studies were omitted from Table I, the first one because the results in the infant group differed considerably from those of other investigators and suggested that there is more rapid urinary excretion of the drug than has been noted by other workers[1, 17] and the second one because of the unusually high doses of digoxin used.[4]

It is apparent from the table that there were significantly higher serum levels in the infants than in the adults.[2, 3, 5] The higher serum concentrations achieved in the infants correlate well with the higher doses administered to them if the dose is calculated per unit of body surface area rather than of body weight (Table II).[5]

In summary, infants absorb and excrete digoxin as well as adults. When higher doses are administered to infants they lead to correspondingly higher serum levels. There is no theory to explain the need for the higher dose in infancy satisfactorily. However, it is possible to speculate that if the heart of an infant has more myocardial Na-K ATPase activity than the heart of an adult, the infant might require more digoxin to inhibit this enzyme and produce a full therapeutic effect.[14]

3. Childhood. The serum concentration of digoxin was found to be the same in toddlers and older children as in adults.[3, 5] This is true despite the fact that the children received almost 100 per cent more digoxin per unit weight as maintenance as did the adults. The half time for elimination of digoxin from the body has only been determined in 3 children to date, but it appears to be similar to that found in infants.[8, 9] Further studies are therefore needed before we can understand the apparent discrepancy between the dose of digoxin administered to children and the steady state serum concentration of the drug in them. It is possible that there is more rapid urinary excretion of digoxin in this age group or that the drug is bound and stored to a greater degree than in the infants. The tissue concentration of digoxin in a 7 year old child was measured and was found to be two- to threefold greater than that found by the same investigators in a 3 month old infant.[8] This observation points to the possibility that the latter theory may have some validity.

4. Dosage schedule. The dosage schedule presently recommended for digoxin therapy of pediatric patients of various ages is summarized in Table III. Note that the recommendation for a total digitalizing dose of digoxin in premature and full term newborn infants is 0.050 mg. per kilogram of body weight. It rises to 0.070 mg. per kilogram of body weight for infants up to 1 year of age and then decreases to 0.060 mg. per kilogram of body weight for 1- to 2-year old infants. It decreases even further for children over the age of 2 years. The recommended dose for these patients is between 0.040 and 0.050 mg. per kilogram of body weight. The maintenance regimen is calculated to replace 20 to 30 per cent of the digitalizing dose per day. If all of the digoxin is given intravenously the total dose should be only 75 per cent of the figures listed above.

Toxicity

Studies in experimental animals indicate that younger animals have a higher tolerance for digitalis glycosides than do adults of the same species. Thus the uniformly

lethal dose (LD_{100}) of glycoside for mature guinea pigs was only 75 per cent of the LD_{100} in newborns and the lethal dose for an isolated and continuously perfused adult Guinea pig heart was 50 per cent of the lethal dose for a heart from a 3 week old animal.[18] Similarly the LD_{100} was significantly lower in adult dogs than in 15 to 65 day old puppies.[19]

It is not possible to determine the effect of age upon the toxicity of a dose of digoxin in the human from the published data. However, it is clear that even in man, toxicity is manifested at lower serum digoxin concentrations in adults than in infants. Signs of digitalis toxicity occur with great frequency in adults and children above the age of 2 years when the serum concentration exceeds 2 ng. per milliliter. Levels below 2 ng. per milliliter are well tolerated.[7,17] It appears that in infants toxicity does not usually occur until the serum concentration exceeds 3.5 ng. per milliliter, so long as acid base balance and electrolyte concentration are normal.[2,3,5] It must be kept in mind, however that many of the early signs of digitalis intoxication (e.g., nausea, vomiting, visual disturbances) are difficult to perceive in infants.

The electrocardiographic signs of digitalis toxicity in infants are more likely to involve conduction impairment and supraventricular arrhythmia and not the ventricular arrhythmias seen in adults.

The following regimen is recommended for serious digoxin toxicity in infants and children.

1. Discontinue further digoxin.
2. If the excessive dose was given intramuscularly, apply cold compresses and tourniquet to the extremity. If an excessive dose was administered by mouth gastric lavage should be attempted.
3. Potassium 0.05 mEq. per kilogram of body weight should be given intravenously over 1 hour. The concentration of the solution in which it is administered should not exceed 80 mEq. per liter. This dose may be repeated after 1 hour, if necessary.
4. Isoproterenol (1 vial = 200 mcg. in 200 c.c. D_5W). Approximate dose up to 10 kilograms body weight 1 to 2 mcg. per minute. 30 kilogram patient 2 mcg. per minute. May be administered in cases of complete A-V block. External pacing may be necessary in such cases.
5. Diphenylhydantoin (2 to 3 mg. per kilogram of body weight) may be administered intravenously in cases of tachyarrhythmias as a stat dose. A continuous infusion may be used if rapid rhythm recurs.
6. Lidocaine (1 mg. per kilogram of body weight). propranolol (0.025 mg. per kilogram of body weight) intravenously may be effective. This can be repeated ×2 after five minute intervals, if no response occurs. Procainamide (3 to 5 mg. per kilogram of body weight slowly intravenously) may be administered in cases of refractory tachycardias.
7. Cardioversion should be used if all other measures fail.
8. Blood should be drawn for determination of the concentration of digoxin.

Attempts to remove the drug by hemodialysis or by peritoneal dialysis have been unsuccessful and such procedures should not be relied upon in these cases.[7]

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Annotations

Ischemic cardiomyopathy

The main function of a physician is to render high quality service to his patients This he must do at a time when medical knowledge is extremely limited for most diseases anyway For example among the frequently encountered cardiac illnesses are *the cardiomyopathies* the most resistant cardiac dis eases to modern therapy Therefore the most re warding therapy for this group of illnesses is pre vention However regardless of all attempts to prevent cardiomyopathies patients develop *these forms of cardiac* disease and their physicians are challenged with management *After all* the cardio-myopathies repre ent expressions of damage to the myocardium the source of pumping power for the circulation And the blood must flow *adequately or death ensues*

Accepting the term cardiomyopathy literally to mean heart muscle pathology the physician in America is confronted with myocardial *ischemia* due to coronary arterial obstructive disease as the most common cause of cardiac muscle pathology in America today The late and readily recognized stage of the disease reveals all the symptoms *and signs* of the syndrome of cardiomyopathy such as congestive heart failure functional systolic murmurs (usually mitral and tricuspid) protodiastolic gallop rhythm and relatively high diastolic blood pressure in addition to the well known manifestations of coronary artery disease The patients have *evidence* of myocardial ischemia such as that of angina pec toris without or with one or more myocardial in farcts This classical syndrome of cardiomyopathy in patients with myocardial ischemia is *often* er roneously considered to be a cardiomyopathy due to other or unknown causes However being aware that the syndrome can be produced by ischemic heart disease it is easy to recognize the cardiomyopathy as being due to myocardial ischemia and the patient can be properly and promptly treated accordingly This syndrome I have chosen to call ischemic car diomyopathy Surely other cardiac diseases myo-cardial or otherwise may be superimposed upon it

Patients with the late stages of ischemic cardio-myopathy require astute and meticulous manage ment in order to achieve the best possible results And many such patients must lead the life of a cardiac invalid or semi invalid to remain alive It is unfortunate that this cour e is often necessary but the physician and the patient have no other choice and the sooner this way of life is thoroughly accepted by both the better the results and the happier the patient will be

Finally it behooves the physician to recognize ischemic heart disease early as well as potential evidence of the disease before it develop in order to institute the best measures of prevention and management to interrupt or delay the onset of the late stages of ischemic cardiomyopathy It should be realized that heart muscle pathology due to is-chemia has a beginning and the beginning may be merely a slightly abnormal shape and/or magnitude of the T wave of the electrocardiogram in a patient who the physician decides from clinical data has potential or early coronary artery disease Proper management of such patients immediately deliber ately and adequately when first seen with angina pectoris or myocardial infarction is necessary for the best treatment and for prevention of advanced ischemic cardiomyopathy with its late and irreversi ble stages of the disease

In the best interest of prevention of extensive and irreversible myocardial damage it must be remem bered that cardiomyopathy can be extremely mild The so-called classical syndrome reflects severe and irreversible damage to the myocardium There-fore the diagnosis of ischemic cardiomyopathy should always be made when the diagnosis of is chemic heart disease is made And when any disease exists in a patient which may result in coronary artery disease or when coronary artery disease is developing it behooves the physician to make the diagnosis of potential ischemic cardiomyopathy The physician then should apply all measures avail able to him to reverse or arrest the coronary heart disease and/or at least reduce the work of the heart so that the myocardial demands for blood do not exceed the ability of the coronary circulation to satisfy those demands

It is realized that some cardiologists limit the term cardiomyopathy to heart muscle disease of unknown cause This practice is not to be ignored but it does restrict the physician and tend to confuse him from the more practical point of view of advising patients and it ultimately influences management *of patients* A more detailed interpretation and classification of the cardiomyopathies is of greater value to the physician who is confronted daily with all sorts of diseases in his many patients

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The nitroblue-tetrazolium dye test and infection in the renal patient

The important observation that polymorphonuclear leukocytes are capable of spontaneously reducing the dye nitroblue tetrazolium (NBT) was made in 1968 by Park and co-workers[1] The absolute number and percentage of circulating granulocytes reducing the dye increases during most bacterial infections and remains unchanged in the presence of viral infection Since this initial report several large studies have confirmed the usefulness of this unstimulated NBT test in the detection and confirmation of bacterial infections in both children and adults[2-4] However there have been a paucity of studies on the usefulness of the NBT test in clinical conditions which carry a high risk of infection one such area is renal disease Specifically there had been no studies on the efficacy of the NBT test in the differential diagnosis of infections in uremics or in immunosuppressed renal transplant patients Consequently we undertook the following study[5]

Two groups of renal patients were selected The first group consisted of 32 uremic patients on whom NBT tests were performed randomly during their illness Twenty seven of these patients were receiving chronic hemodialysis and none was receiving immunosuppressive therapy The second group comprised ten post renal transplant patients 8 of whom were monitored serially with the NBT test following their transplants We attempted to assess the usefulness of this test in the early diagnosis of bacterial infection and in its ability to differentiate infection from rejection All of the transplant patients were receiving azathioprine (Imuran) at a uniform dosage of 2 mg per kilogram of body weight and steroids as Prednisolone at doses of 10 mg to 1 000 mg daily

In our uremic group 23 of 32 patients were uninfected when NBT testing was performed The mean value of NBT reduction in these patients was 5 1 per cent (i e 5 1 per cent of the polymorphonuclear leukocytes reduced NBT dye) The range was 0 to 15 per cent The remaining nine patients in this group had documented infection 3 viral and 6 bacterial The individuals with viral infection had normal NBT reduction (1 to 8 per cent) and of those with documented bacterial infection 5 of 6 had markedly elevated reduction of the dye (all greater than 40 per cent)

In our group of ten post transplant patients seven had proved bacterial infection at some time during their course All of these showed significantly elevated NBT positivity (31 to 55 per cent) at times of infection Four documented rejection episodes uncomplicated by concurrent infection occurred in 3 of the patients. During these episodes NBT reduction remained in the normal or uninfected range. One patient in the group of ten had an uncomplicated postoperative course and his NBT values remained normal on serial sampling When Imuran and large doses of steroids (as much as one gram of Prednisolone daily) were administered we found that the leukocytes of bacterially infected patients were capable of responding with increased dye reduction despite some previous suggestions to the contrary[4,6] The latter two studies measured NBT dye reduction in phagocytosing rather than in resting cells whereas our method quantified spontaneous dye reduction in non phagocytosing cells.

We were able to conclude from these findings that the NBT test is a valuable device for monitoring the infectious disease status of the renal patient We base this conclusion on the following points (1) Non infected uremic patient have normal baseline NBT values and in the face of bacterial infection are capable of mounting a positive NBT response The test was also capable of distinguishing the viral from the bacterial infection despite similar clinical presentation (2) Renal transplant patients are capable of responding to bacterial infections with a marked increase in the percentage of NBT positive cells This is true in spite of the administration of large doses of steroids (3) NBT test values remain normal in acute rejection allowing one to differentiate between bacterial infection and rejection even though the clinical presentations are so similar

This study would also suggest by extrapolation that the NBT test is a valuable adjunct in following any patient whose underlying disease or therapy makes him especially susceptible to severe infection confirmation of the test s validity in any particular disease entity is a necessary prerequisite however

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The magnitude of risk of developing complete heart block in patients with LAD-RBBB

In recent years, the electrocardiographic (ECG) association of left axis deviation with right bundle branch block (LAD-RBBB) has been recognized as a manifestation of bilateral bundle branch disease[1,6] and as a common forerunner of complete heart block.[3,6,11] In spite of the great number of papers dealing with this topic that have appeared in the recent literature, a question of the utmost importance still remains unanswered: what is the exact magnitude of the risk of development of complete heart block in patients with LAD-RBBB? This risk has been estimated by previous workers (6 per cent,[3] 9 per cent,[10] 10 per cent,[8] and 13.6 per cent[11]), but to our knowledge it has not been discussed so far in terms of duration of follow-up.

The purpose of the present annotation is to report our experience in this matter. The ECG files of 50 patients who were seen initially at our hospital in 1968 or 1969 have recently been reviewed. Reasons for selecting these patients were as follows. All had an ECG which fulfilled previously described criteria for left anterior fascicular block combined with right bundle branch block.[6,12] None had evidence of atrioventricular conduction disturbance on the causal ECG taken at their first visit. Cases with myocardial infarction, congenital cardiac malformations, and valvular heart disease were excluded. In our selected patients, the underlying lesions responsible for the conduction disturbances were thought to be a sclero-degenerative process (Lenègre's or Lev's disease).[6]

The group under study consisted of 34 men and 16 women ranging in age from 43 to 83 years with an average age of 66 years. Several of these patients already had serial ECG tracings in their personal records when they were first examined in our hospital. This fact permitted a retrospective extension of the follow-up periods. The patients were all repeatedly checked later and received particularly close scrutiny. At each examination they were carefully interviewed. If any symptom suggestive of paroxysmal atrioventricular block was discovered (episodes of dizziness, syncope, or seizures) and if the ECG failed to disclose any atrioventricular conduction disturbance, the patient was admitted to the intensive care unit and the ECG was continuously monitored for various periods of time up to 96 hours. Though tedious and expensive, this procedure revealed rewarding findings in several instances.[1]

Altogether, 16 patients (32 per cent) were discovered to present with transient or permanent complete A-V block at some time in their illness. They were all treated by transvenous demand pacemakers. It should be stressed that in 8 of these 16 instances complete A-V block was identified during the first 12 months of follow-up. Actually, these eight patients already had suggestive complaints at the time of their initial visit. Their presence in the series accounts for the skewing of the data towards abnormally high percentages of complete A-V block of early onset. Therefore, the most interesting data of this study are concerned with 38 patients of the series who had a follow-up duration longer than 12 months and who had no dizziness or syncope when they were first seen. In the latter group, follow-up tracings were available for as long as 11 years, with an average period of 4.8 years. To evaluate the long-term prognosis of the association LAD-RBBB, our data were statistically treated using a method similar to the "life table method" proposed by Merrel and Shulman (1955).[13] The expected incidence of A-V block was calculated for each duration of follow-up (Fig. 1). From the figures thus obtained, it appears that the risk of developing complete heart block is about 6 per cent per year of follow-up after recognition of LAD-RBBB.

These results deserve some comments. To begin with, the total incidence of complete A-V block observed in our patients (21 per cent) appears somewhat higher than that quoted in previous reports.[3,8,10,11] Two reasons might account for this discrepancy. Firstly, the mean duration of follow-up in our series (4.8 years) was comparatively longer than in others (6.3 months[10] and 19 months[11]). Secondly, the period under scrutiny started in 1968, at a time when one was already very eager to try and identify paroxysmal A-V block in patients with LAD-RBBB.

As predicted by Ranganathan and co-workers,[14] the risk of complete heart block appears extremely high when plotted with increasing time. This finding meets with the opinion expressed by Blondeau and Lenègre[15] that if one excludes cases with myocardial

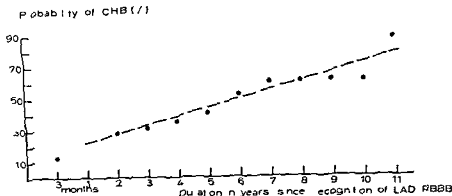


Fig *1* Risk of development of transient or permanent complete heart block in patients with LAD RBBB The expected incidence of complete heart block was calculated for each duration of follow up using a method similar to that proposed by Merrel and Shulman (1955)[11] If one only considers the portion of the diagram which covers from 1 to 11 years of follow up (38 cases) the risk of developing complete heart block may be estimated at 6 per cent per year of follow up after identification of LAD RBBB ($y = 5\ 96x + 22\ 3$)

infarction and congenital cardiac malformations the natural outcome of patients with LAD RBBB is sooner or later towards complete A V block in approximately 100 per cent of the cases

Nonetheless the duration in years that elapses between the first time LAD RBBB is recogni ed and the onset of complete A V block varies considerably in all published series *In some observations*[14] *it was* even as long as 23 years This remark leads to a di rect practical conclusion At the present time any *indiscriminate* tendency *to* pace all patients with LAD RBBB as soon as this pattern is recognized appears unjustified So far our policy in such cases has always been to await the first signs of paroxysmal A V block before implanting a cardiac pacemaker This attitude admittedly debatable will possibly be reconsidered after completion of prospective studies of patients with LAD RBBB by means of His bundle electrography and atrial pacing It is to be hoped that such investigations in progress in this institution as well as in many others will help identify at an early stage those patients who would be at greater risk for subsequent appearance of A V block and who might benefit from preventive pacing [4 16]

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The magnitude of risk of developing complete heart block in patients with LAD-RBBB

In recent years the electrocardiographic (ECG) association of left axis deviation with right bundle branch block (LAD RBBB) has been recognized as a manifestation of bilateral bundle branch disease[1-6] and as a common forerunner of complete heart block[2-11] In spite of the great number of papers dealing with this topic that have appeared in the recent literature a question of the utmost importance still remains unanswered what is the exact magnitude of the risk of development of complete heart block in patients with LAD RBBB? This risk has been estimated by previous workers (6 per cent[9] 9 per cent[10] 10 per cent[8] and 13 6 per cent[11]) but to our knowledge it has not been discussed so far in terms of duration of follow up

The purpose of the present annotation is to report our experience in this matter The ECG files of 50 patients who were seen initially at our hospital in 1968 or 1969 have recently been reviewed Reasons for selecting these patients were as follows All had an ECG which fulfilled previously described criteria for left anterior fascicular block combined with right bundle branch block[1-12] None had evidence of atrioventricular conduction disturbance on the causal ECG taken at their first visit Cases with myocardial infarction congenital cardiac malformations and valvular heart disease were excluded In our selected patients the underlying lesions responsible for the conduction disturbances were thought to be a sclero degenerative process (Lenègre s or Lev s disease)[3]

The group under study consisted of 34 men and 16 women ranging in age from 43 to 83 years with an average age of 66 years Several of these patients already had serial ECG tracings in their personal records when they were first examined in our hospital This fact permitted a retrospective extension of the follow up periods The patients were all repeatedly checked later and received particularly close scrutiny At each examination they were carefully interviewed If any symptom suggestive of paroxysmal atrioventricular block was discovered (episodes of dizziness syncope or seizures) and if the ECG failed to disclose any atrioventricular conduction disturbance the patient was admitted to the intensive care unit and the ECG was continuously monitored for various periods of time up to 96 hours Though tedious and expensive this procedure revealed rewarding findings in several instances[1]

Altogether 16 patients (32 per cent) were discovered to present with transient or permanent complete A V block at some time in their illness They were all treated by transvenous demand pacemakers It should be stressed that in 8 of these 16 instances complete A V block was identified during the first 12 months of follow up Actually these eight patients already had suggestive complaints at the time of their initial visit Their presence in the series accounts for the skewing of the data towards abnormally high percentages of complete A V block of early onset Therefore the most interesting data of this study are concerned with 38 patients of the series who had a follow up duration longer than 12 months and who had no dizziness or syncope when they were first seen In the latter group follow up tracings were available for as long as 11 years with an average period of 4 8 years To evaluate the long term prognosis of the association LAD RBBB our data were statistically treated using a method similar to the life table method proposed by Merrel and Shulman (1955)[13] The expected incidence of A V block was calculated for each duration of follow up (Fig 1) From the figures thus obtained it appears that the risk of developing complete heart block is about 6 per cent per year of follow up after recognition of LAD RBBB

These results deserve some comments To begin with the total incidence of complete A V block observed in our patients (21 per cent) appears somewhat higher than that quoted in previous reports[8-11] Two reasons might account for this discrepancy Firstly the mean duration of follow up in our series (4 8 years) was comparatively longer than in others (6 3 months[10] and 19 months[11]) Secondly the period under scrutiny started in 1968 at a time when one was already very eager to try and identify paroxysmal A V block in patients with LAD RBBB

As predicted by Ranganathan and co-workers[14] the risk of complete heart block appears extremely high when plotted with increasing time This finding meets with the opinion expressed by Blondeau and Lenègre[15] that if one excludes cases with myocardial

Each subject was given 1 Gm sulfadimidine intravenously and at the same time an intravenous infusion of Inulin containing 10 to 25 Gm was started and continued for 4 hours Blood and urine samples were taken before and 2 3 and 4 hours after the injection of sulfadimidine and blood samples were taken 24 hours after the injection Inulin was measured by Bojesen s method and sulfadimidine and N acetylated sulfadimidine were estimated by the method of Bratton and Marshall[6]

We found Inulin clearance as well as the mean clearances of sulfadimidine much lower in all uremic patients than in the controls

Since only the non protein bound sulfadimidine can be filtered through the glomeruli it was estimated by ultrafiltration through a cellophane membrane Table I shows that although the total plasma concentrations of sulfadimidine are comparable in the two groups the non protein bound *sulfadimidine concentrations* are higher in the uremic group This accords with other findings[7,8] The explanation is not known The lesser protein *binding of sulfadimidine in uremia* should favor the excretion of the drug in uremic patients nevertheless the excretion of the drug is lower in uremic subjects *than in controls*

Acetylated sulfadimidine constituted 43 per cent of the total plasma sulfadimidine in the uremic group *and 21 per cent in the controls for urine the figures were 38 per cent in the uremic patients and 52 per* cent in the controls. Similar observations have been described[3] The higher percentage *of acetylated* sulfadimidine in plasma than in urine of uremic *subjects indicates* a lower renal excretion of acetylated sulfadimidine rather than an increased acetylation

It has been shown that sulfadimidine in the human kidney is subjected to filtration and active tubular excretion as well as tubular reabsorption[9] Our data do not allow an estimation of any active secretion but the ratios between non protein bound sulfadimidine clearance and Inulin clearance show that tubular reabsorption occurs in uremic as well as normal subjects The parallel correspondence between Inulin clearance and non protein bound sulfadimidine clearance however indicates that *reduced filtration* is mainly responsible for the decrease in sulfadimidine excretion in *kidney failure* This explains too the finding that 24 hours *after the* injection of sulfadimidine between 7 and 23 mcg sulfadimidine per milliliter was still found in the plasma of uremic subjects whereas none could be found in plasma from controls This is in agreement with the demonstration of the 2 to 3 times longer plasma half lives of sulfadimidine methoxypyridazine sulfadimethoxine and Sulfadoxine in uremic subjects *than in normal persons*[1] Our results also agree with those of Sharpstone[4] who demonstrated reduced excretion of sulfamethoxazole as well as trimethoprim in kidney *failure On the other hand* our findings are at variance with those of Williams and associates[3] No explanation for this discrepancy can be offered

We conclude that there is a definite risk for an accumulation of the drug when uremic patients are treated with sulfadimidine

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Renal excretion of sulfadimidine in normal and uremic subjects

The renal excretion rate of sulfonamides is an important factor in determining the concentrations of sulfonamides attainable in the body and in the urine The restrictions imposed on antibacterial drugs in the treatment of patients with chronic renal failure have been described [1] However the renal excretion of sulfonamides in chronic renal failure has only been studied by a few workers [2,4]

A higher renal clearance of sulfadimidine in uremic patients than in controls have been reported[1] —a surprising result which could have important therapeutic implications Since sulfonamides are still used in clinical practice and may even gain in importance with the introduction of trimethoprim we decided to compare the renal clearances of sulfadimidine and Inulin in 10 normal and 10 uremic per on

Table I Data on 10 uremic subjects and 10 controls

Patient	Age (yr)	Sex	Body weight (Kg)	Urine flow rate (ml/min)	Inulin clearance (ml/min)	Plasma sulfadimidine (µg/ml)		Total sulfadimidine urine concentration (µg/ml)	Sulfadimidine clearance (ml/min)	
						Total	Unbound		Bound	Unbound
Uremic*										
1	69	F	70	1 7	5	27	10 5	31	2 0	5 0
2	68	M	90	2 0	5	19	7 4	11	1 2	3 0
3	61	M	74	1 9	6	16	6 2	12	1 4	3 7
4	56	F	62	2 4	7	48	18 7	32	1 6	4 1
5	70	F	55	0 7	9	56	21 8	85	1 1	2 8
6	67	M	48	0 7	10	31	12 1	145	3 2	8 4
7	74	F	50	0 9	14	42	16 4	80	1 7	4 4
8	46	F	46	4 3	23	35	13 7	22	3 0	6 9
9	53	M	62	4 7	33	37	14 4	28	3 6	9 1
10	26	M	79	4 5	49	45	17 6	52	5 2	13 3
Controls										
1	46	M	71	10 0	131	66	9 9	36	5 5	36 4
2	27	F	57	3 6	100	36	5 4	73	7 3	48 7
3	33	M	84	6 5	122	47	7 1	61	8 4	56 0
4	43	F	65	5 9	123	30	4 5	61	12 0	49 9
5	40	M	65	3 2	115	35	5 3	91	8 3	54 9
6	32	F	54	5 9	110	46	6 9	75	9 6	64 1
7	23	M	71	8 3	122	50	7 5	49	8 1	54 2
8	27	F	48	8 7	112	27	4 1	32	10 3	67 9
9	27	F	72	5 5	125	46	6 9	86	10 3	68 5
10	26	M	74	7 2	122	54	8 1	41	5 5	36 4

*Patients 1 and 3 and 8 to 10 had chronic glomerulonephritis and patients 2 and 4 to 7 had chronic pyelonephritis

retically it is believed that all visceral functions can be brought under voluntary control by prolonged yogic training but perhaps their most fascinating claim has been the ability to stop the heart at will However in most instances where this has been investigated so far it has turned out to be an exaggerated Valsalva maneuver in some form which makes the pulse and heart sounds imperceptible while the heart continues to beat at a slow rate[1 2]

Recently we had the rare opportunity of investigating an altogether different and very interesting demonstration of this supposed yogic control over the heart Yogi Satyamurti a sparsely built man of about 60 years of age remained confined in a small underground pit for 8 days in what according to him was a state of Samadhi or deep meditation with all bodily activity cut down to the barest minimum The pit was a 1 5 meter cube dug out in an open lawn surrounded by the Medical Institute buildings and was completely sealed from the top by bricks and cement mortar The Yogi squatted on the floor of the pit with nothing on except a light cotton garment About 5 liters of water was placed in one corner presumably for drinking but according to the Yogi only for keeping the air fully humid An ECG (Lead II) was continuously monitored durin these 8 days and various other laboratory investigations were carried out before and after The ECG leads were kept short enough not to allow any free movement inside the pit

The 12 lead ECG recorded before closing the pit was within normal limits (Fig 1 *strip A*) but a significant sinus tachycardia developed soon after It increased progressively reaching a heart rate of 250 per minute on the second day (Fig 1 *strip B*) At 5 15 P M on the second day when the Yogi had been inside for about 29 hours to our great surprise a straight line replaced the ECG tracing (Fig 1 *strip C*) There was no electrical disturbance of any sort even at higher amplification and with different leads There had been no slowing of the heart or signs of ischemia preceding this

The straight line on the ECG persisted till the eighth morning Then to our astonishment electrical activity returned about half an hour before the pit was scheduled to be opened After some initial disturbance a normal configuration appeared Although some sinus tachycardia was still there there was no other significant abnormality (Fig 1 *strip D*) The Yogi had informed us beforehand that he would begin to come out of his deep trance or suspended animation after nearly 7 days much in the same way that a normal person wakes up after a few hours sleep

When the pit was opened on the eighth day the Yogi was found sitting in the same posture One of us immediately went in to examine him He was in a stuporous condition and was very cold (oral temperature was 34 8 C) On being taken out of the pit he developed severe shivering and this persisted for nearly 2 hours A 12 lead ECG repeated in the laboratory subsequently was again within normal limits (Fig 1 *strip E*)

The Yogi and his admirers felt more than satisfied at this scientifically documented proof of a remarkable Yogic feat while we were left rather perplexed and confused We were expecting some bradycardia

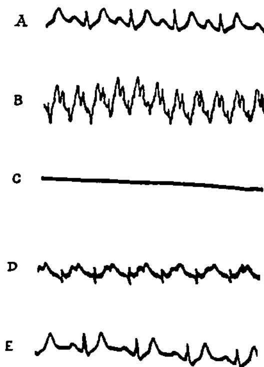


Fig *1* ECG tracing of the Yogi Lead II (*Panel A*) first day at 11 00 A M one hour before closing the pit Normal sinus rhythm Heart rate was 106 per minute PR interval was 0 16 second QRS interval was 0 08 second and there was an upright T wave (*Panel B*) second day at 5·00 P M Severe sinus tachycardia with a heart rate of 250 per minute a PR interval of 0 12 second a QRS interval of 0 06 second and a high uptake of the ST segment (*Panel C*) second day at 6·00 P M There is a straight line with no electrical disturbance This continued for the next 5 days (*Panel D*) eighth day at 7.30 A M half an hour before opening the pit Sinus tachycardia is in evidence with a heart rate of 142 per minute slightly prolonged PR interval of 0 20 second a QRS interval of 0 06 second and an upright T wave (*Panel E*) eighth day at 10 00 A M two hours after coming out of the pit The tracing is normal with a heart rate of 98 per minute PR interval of 0 16 second a QRS interval of 0 08 second and an upright T wave

and possible signs of myocardial ischemia but contrary to this there was severe tachycardia followed by a complete disappearance of all complexes Any instrumental failure was ruled out by thoroughly checking the machine and also by the spontaneous reappearance of the ECG on the last day A disconnection of the leads by the Yogi quite a likely explanation ought to have given rise to considerable electrical disturbance but there was hardly any Later on we tried all sorts of manipulations with the leads to simulate what the Yogi could have done

Letters to the Editor

Cardioversion after valve replacement

To the Editor

I read with interest the annotation by Drs Jenzer and Lown dealing with cardioversion after valve replacement (AM HEART J 84 840 1972) In reading it it became obvious that the authors have omitted reference to two critical issues Unless such information is provided their comments and recommendations lose most of their relevance These issues are

1 How many of the 102 patients with valve replacement and the 58 patients with mitral valvotomy developed atrial fibrillation after the operation?

2 How many patients who were successfully cardioverted remained in sinus rhythm for more than two months?

We have demonstrated[1,2] and others have amply confirmed our observations that postoperative atrial fibrillation and atrial fibrillation *present prior* to mitral valve surgery are two entirely different conditions The former is an acute reaction to surgical trauma that bears no relation to the underlying disease (it occurs not only after cardiac but also after pulmonary operations) and is virtually 100 per cent convertible to sinus rhythm The latter is a specific complication of mitral valve disease one that eventually leads to anatomic damage of atrial musculature[3] Our series showed a success rate in post operative conversion of patients in the *second* category of 77 per cent but more than half of these lapsed back into atrial fibrillation after varying periods of time

If an article describes the value of cardioversion and we recognize that cardioversion is good for oranges but only fair for apples shouldn t we know how many apples and oranges were mixed in the basket?

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Reply

To the Editor

Dr Selzer raises questions not germane to the intent of our brief communication The objective was simply to provide evidence that valve replacement does not diminish the efficacy of cardioversion in restoring atrial fibrillation to sinus rhythm furthermore it was to demonstrate that in these patients the procedure is not fraught with an increased incidence of immediate or late complications If the physician therefore believes that sinus rhythm needs to be re established cardioversion affords a simple safe and effective method

Of course Dr Selzer s questions can be factually answered Of the 102 patients with valve replacement 19 developed atrial fibrillation for the first time after the operation The success rate of cardioversion and the required energy were the same irrespective of when the arrhythmia first occurred Our experience to date indicates that if atrial fibrillation has been present for less than one year prior to valvular surgery the likelihood for sustained sinus rhythm for the ensuing year approximates 50 per cent

We are of course well aware that sinus rhythm has a greater chance of being maintained in patients in whom atrial fibrillation follows rather than precedes valvular operation The crucial question therefore is which patient following valve correction will maintain sinus rhythm after cardioversion when the arrhythmia has been established for some months We are not aware of any clinical shibboleth to permit sush distinction In the absence of guide lines we believe that all such patients should be subjected to the relatively innocuous procedure of cardioversion Whether the arrhythmia merely precedes or follows valvular operation is far too simple and inadequate a discriminant Dr Selzer hails from a state well known for the abundance and variety of its fruit he should therefore have no difficulty in distinguishing apples from oranges

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The Yogic claim of voluntary control over the heart beat an unusual demonstration*

To the Editor

Yogis in India have long been reputed to develop a remarkable control over bodily functions Theo-

*A detailed report on the Yogi is appearing in *The Indian Journal of Medical Research* November 1973

Table I. Effectiveness of practolol in 145 patients

Type of arrhythmia	No digitalis			Previous digitalis		
	No	Good result	No result	No	Good result	No result
Sinus tachycardia	10	9	1	21	18	3
Atrial fibrillation	21	15	6	25	24	1
Atrial flutter	22	10	12	14	12	2
Atrial tachycardia	17	12	5	15	14	1

2 *Atrial fibrillation (7 patients)* normal sinus rhythm (N.S.R.) in 1 slowing of the H R in 5 (average reduction ≈ 35 per cent) no result in 1

3 *Atrial flutter (4 patients) N S R in 1 (after a* short sequence of atrial fibrillation) slowing in 2 (average reduction = 32 5 per cent) no result in 1

4 *Supraventricular tachycardia (5 patients)* N.S R in 3 slowing in 1 (reduction = 38 per cent) no result in 1

5 Ventricular ectopics (3 patients) total disappearance in 1 decrease in 1 no result in 1 Good results (N.S R or H R below 100 beats per minute) were thus obtained in 88 4 per cent of the patients with supraventricular tachyarrhythmias In none of these acutely ill patients did worsening of the respiratory status occur during or within 15 minutes after drug administration.

The antiarrhythmic effectiveness of practolol is markedly potentiated by previous digitalization (Table I) In 70 patients with supraventricular tachyarrhythmias of various etiology practolol used alone was effective in 46 (67 per cent) 24 patients (33 per cent) did not re pond at all In a similar group of 75 patients who had been previously digitalized good results were obtained in 68 (90 7 per cent) 7 patients only (9 3 per cent) did not re pond at all

We do feel as did Dr Fromgren that practolol may be used safely in patients with bronchospasm and that it is a drug of choice for the treatment of supraventricular tachyarrhythmias complicating their respiratory insufficiency

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Right atrial electrocardiogram resulting in hemopericardium

To the Editor

In a recent communication Drs Homesley and Zelenik re-emphasized the potential hazards of routine investigations (AM HEART J 84 135 1972) We would like to stress again this point by reporting briefly a case of lethal hemopericardium which occurred as a result of a right atrial electrocardiogram (RAE) A 61 year old man was admitted to our department because of the recent onset of heart failure and supraventricular tachycardia The RAE was recorded through a Vigon catheter to further investigate the arrhythmia. The procedure went uneventfully but seven hours later seizures occurred suddenly while blood pressure dropped The patient became cold and cyanotic Distension of the neck veins appeared He was given 40 mg of metaraminol which failed to bring up the blood pressure Three more seizures occurred within an hour The patient became unconscious as a slow junctional rhythm was recorded Attempts at resuscitation were ineffective Pathological studies revealed a traumatic perforation of the right atrium wall which resulted in a fatal acute tamponade.

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Atrial ectopic tachycardia

To the Editor

I read with much interest the article by Goldreyer Gallagher and Damato in a recent issue of the JOURNAL (AM HEART J 85 205 1973)[1] Again these excellent ongoing studies from their laboratory have demonstrated the utility of intracardiac recording techniques for the evaluation of potential electrophysiologic mechanisms of supraventricular

inside the pit (notwithstanding the total darkness and his ignorance of ECG technique) but in every case there was marked disturbance. Therefore, although it is obviously difficult to believe that the Yogi could have completely stopped his heart or decreased its electrical activity below a recordable level, we still had no satisfactory explanation for the ECG tracings before us.

Apart from this, the Yogi had of course endured total starvation, sensory deprivation, as well as the discomfort of a very humid, closed atmosphere for 8 days. We did not pay much attention to anoxia, thinking that sufficient ventilation could occur through the bare earth on the sides of the pit. The loss of weight (4.5 kilograms) and other biochemical changes were essentially the same as can be expected in starvation under similar conditions. They certainly discount any remarkable depression of the metabolic rate.

The more optimistic amongst us considered this feat to be a marvelous extension of the "hypometabolic wakeful state of yogic meditation" as described by Wallace and co-workers[3] and the conditioned learning of autonomic responses in rats reported by DiCara.[4] The skeptics, however, were inclined to take the whole thing as some cleverly disguised trick. But for the present we only want to put this interesting experiment on record just as an intriguing and inconclusive attempt of a Yogi to demonstrate a voluntary control over his heart beat.

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Atropine in acute myocardial infarction

To the Editor:

The discussion of the value of atropine in acute myocardial infarction at the last meeting of the American College of Cardiology in San Francisco (Medical World News, March 9, 1973) is the reason for the following comments.

The risk of giving atropine in patients with coronary disease has been demonstrated many years ago by Wayne and Laplace.[1] They found in patients with angina pectoris that after administration of atropine a lesser physical exertion elicited anginal pain. Scherf and Schnabel[2] demonstrated that following an intravenous injection of 2 mg. of atropine in patients with syphilitic aortitis and angina pectoris due to stenosis of the orifice of a coronary artery, anginal pain with marked depression of the RS-T segments appeared. The increased rate induced by atropine in many (not all) patients with coronary disease is responsible for these results. This is illustrated by another observation reported by the same authors. A diabetic patient died several minutes after the intravenous injection of ¾ mg. of atropine. The autopsy revealed severe arteriosclerosis of both coronary arteries.

Because the appearance of a marked increase of rate following an injection of atropine cannot be predicted, I consider this medication risky in patients with coronary disease.

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Practolol in treating tachyarrhythmias

To the Editor:

We read with great interest the article of Dr. H. Formgren entitled "Practolol in the treatment of tachyarrhythmias in patients with bronchial asthma" (Am. Heart J. 84:710, 1972). We would, however, like to take issue with his statement that "Practolol has not been previously given to asthmatics for treatment of concomitant cardiovascular disorder."

Since 1969 we have indeed been using practolol for the treatment of acute tachyarrhythmias and have reported our results previously.[1,2] We would therefore like to report briefly our experience in patients with bronchospasm due to asthma bronchiale or chronic obstructive lung disease.

When assessing the antiarrhythmic effectiveness of a drug we feel that it always should be given intravenously and under continuous electrocardiographic recording. Practolol was given as follows: 5 mg. every minute until a therapeutic result was obtained or a total dose of 25 mg. was reached; if necessary, a maintenance dose of 100 to 200 mg. twice daily was given.

The results obtained in 29 patients hospitalized with acute respiratory failure can be summarized as follows:

1. Lowering of the heart rate (H.R.) below 100 beats per minute (average reduction = 31.7 per cent) in 10 patients with sinus tachy-

Book reviews

ECHOCARDIOGRAPHY By Harvey Feigenbaum M D and Sonia Cheng B.S Philadelphia Pa 1972 Lea & Febiger 239 pp

Feigenbaum has rendered an extremely valuable service to cardiology in this lucid and practical publication on echocardiography The book is well written and well organized The presentations are designed for beginners and the subjects discu sed are extremely well selected This book presents very well the present state of clinical echocardiography a rapidly changing field in cardiology All cardiologist internists and students hould study this book and learn echocardiography now and continue their education from the medical literature This excellent well written book by an authority is highly recommended

TREATMENT OF HEART DISEASE IN THE ADULT 2nd ed By Ira Lloyd Rubin M D Harry Gross M D and Sidney R Arbeit M D (Clinical Pharmacology) Duncan E Hutcheon M D Philadelphia Pa 1972 Lea & Febiger 506 pp Price $27 00

This second ed tion on the treatment of heart disease in the adult is a good one The presentations are clear and the subjects of practical nature It contains 20 chapters concerned with coronary heart d sease drugs hypotensi e heart disease and the other common forms of heart disease The authors also discuss endocarditis pericarditis arrhythmias pacemakers digitalis pregnancy and heart disease and other clinical and therapeutic problems related to heart disease The presentations are good The authors lucidly define their therapeutic approaches to heart disease This is a practical and valuable book for practicing physicians as well as for physicians in training

ON PULSATILE AND STEADY ARTERIAL FLOW THE GTS CONTRIBUTION By A Iberall S Cardon and E Young Upper Darby Pa 1973 General Technical Services Inc 225 pp Price $6 00

This small book on pulsatile and steady arterial blood flow emmates from the research of the NASA program on pace medicine The contributors have considered the important factors influencing arterial blood flow from mathematical and engineering points of view These six essays hould interest physiologists rheologists and investigators of the peripheral circulation The authors of the essays have attempted to consider quantitatively the variables that influence arterial flow Their considerations are thought provoking but still fail to define entirely the extremely dynamic changes in the many complex variables that modify the circulation of blood in arteries This is a very good and important publication

arrhythmias This article emphasizes that in addition to re entry ectopic atrial pacemakers may be responsible for paroxysmal supraventricular arrhythmias Furthermore they stress that atrial arrhythmias due to re entry generally require (1) atrial premature depolarizations and (2) AV nodal conduction delay Recent reports however have commented on the fact that paroxysmal re entrant atrial arrhythmias may also occur because of (1) progressive AV nodal conduction delay *without* atrial premature beats and (2) progressive delay in conduction in the *distal conduction system*[2,3] These reports would I am sure add further support to comments that all re entrant atrial tachycardias may not have the same mechanism

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Reply

To the Editor

Drs Mandel Lozano and Hayakawa correctly point out that not all atrial tachycardias are due to re entry and in fact that was the purpose of our recent report[1] Those atrial tachycardias which are due to re entry may be due to re entry via the AV node[2] the distal AV conduction system and possibly the sinoatrial node Our experience however in studying more than 30 patients with classical paroxysmal supraventricular tachycardia has shown the mechanism of the tachyarrhythmia to be due to AV nodal re entry in each case Although other sites of re entry are possible I would stress that AV nodal re entry is the typical mechanism of paroxysmal supraventricular tachycardia

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Systolic time intervals in man

To the Editor

Contrary to the statement of Dr Lindquist and associates[1] we did not correct the PEP for heart rate in our paper[2]

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Reply

To the Editor

We apologize for this error in our paper[1] and note that your data[2] recorded only the QS_2 and LVET corrected for heart rate Had the PEP been similarly corrected by using the regression equations of Weissler and colleagues[3] your normal subjects would have demonstrated a mean decrease of 14 msec with exercise Hence our observations on the significance of protocol and method of heart rate correction for the STI in general are still valid

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Books received

ASTHMA A PRACTICAL GUIDE FOR PHYSICIANS Prepared by a joint committee of the Allergy Foundation of America and the American Thoracic Society Published by the National Tuberculosis and Respiratory Disease Association in cooperation with the Allergy Foundation of America 1973 72 pages

LEARNING HOW TO LIVE WITH HEART TROUBLE By Arthur J Snider Chicago Illinois 1973 Budlong Press Company 125 pages Price $1 75

DEVELOPMENTS IN BIOMEDICAL ENGINEERING Edited by Martin M Black New York 1973 Crane Russak & Company Inc 972 pages Price $19 75

CARING FOR THE DYING PATIENT AND HIS FAMILY A MODEL FOR MEDICAL EDUCATION—MEDICAL CENTER CONFERENCES Edited by Dr Austin H Kutscher and Michael R Goldberg New York 1973 Health Sciences Publishing Corporation 72 pages

PHYSIOLOGY AND BIOPHYSICS DIGESTION METABOLISM ENDOCRINE FUNCTION AND REPRODUCTION 20th ed Edited by Theodore C Ruch Ph D and Harry D Patton Ph D M D Philadelphia 1973 W B Saunders Company 391 pages

THE ALLIED HEALTH PROFESSIONAL AND THE PATIENT TECHNIQUES OF EFFECTIVE INTERACTION By Ruth Purtilo R P T Philadelphia 1973 W B Saunders Company 229 pages

THE CRISIS TEAM—A HANDBOOK FOR THE MENTAL HEALTH PROFESSIONAL By Julian Lieb M B B Ch Ian I Lipsitch M D and Andrew Edmund Slaby M D Hagerstown Maryland 1973 Harper & Row Publishers Inc 186 pages Price $6 95

PROGRESS IN CARDIOLOGY No 2 Edited by Paul N Yu M D and John F Goodwin M D Philadelphia 1973 Lea & Febiger Publishers 290 pages. Price $15 00

ESSENTIALS OF PEDIATRIC CARDIOLOGY By James H Moller M D Philadelphia 1973 F A Davis Company 124 pages Price $4 50

THE MANAGEMENT OF NEONATES AND INFANTS WITH CONGENITAL HEART DISEASE By Donald M Billig M D and Marshall B Kreidberg M D New York 1973 Grune & Stratton Inc 182 pages Price $12 75

ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY Vol 26 PHARMACOLOGICAL CONTROL OF LIPID METABOLISM Edited by William L Holmes Rodolfo Paoletti and David Kritchevsky Proceeding of the Fourth International Symposium on Drugs Affecting Lipid Metabolism held in Philadelphia Pennsylvania September 8 11 1971 New York London 1972 Plenum Press 359 pages Price $22 50

THE HARVARD FATIGUE LABORATORY ITS HISTORY AND CONTRIBUTIONS By Steven M Horvath and Elizabeth C Horvath Englewood Cliffs New Jersey 1973 Prentice Hall Inc 182 pages Price $9 95

THE SILENT DISEASE HYPERTENSION By Lawrence Galton New York 1973 Crown Publishers Inc 210 pages Price $5 95

American Heart Journal

September 1973 Volume 86 Number 3

Editorial

His bundle electrocardiography

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All new techniques introduced into medicine are ultimately judged by their contribution to our understanding of pathophysiology enhancement of diagnostic ability insight into the mechanism of therapeutic interventions *and to the over all* management of the ill patient

The technique of His bundle electrocardiography (HBE) although relatively new has interested many investigators and has resulted in a number of published studies with considerable unanimity of findings For this reason one can attempt to evaluate even at this early stage of the development the contribution of *HBE* to our understanding of the mechanism of arrhythmias and to the management of the patient with heart disease This editorial was written with a *clear understanding* that information inherent in HBE is far from complete and that much of it is yet to be realized

The technique of HBE involves passing a catheter across the tricuspid valve which requires sophisticated and expensive instrumentation and considerable technical skill However in experienced hands the technical aspects *of the procedure* are relatively simple and safe An electrode catheter is introduced percutaneously into the femoral vein with its tip positioned near the septal leaflet of the tricuspid valve The His potential (H) appears as a well *defined most often bipolar spike* between the low atrial (A) and ventricular (V) electrograms The interval between the earliest onset of the surface P wave or a high right atrial deflection and the low right atrial deflection (P A) is a measure of intra atrial conduction The interval between A and H (A H) is a measurement of the conduction across the A V node and varies in *duration from 50 to 120 msec* depending on the cycle length and autonomic influences The interval from H to V (H V) is a measure of His Purkinje conduction time and is determined by the interval between the His deflection and the earliest ventricular activity recorded in any lead The HV interval is a measure of conduction through the His bundle distal to the recording electrode the bundle branches and the Purkinje system up to the point of ventricular activation In contrast to a relatively wide range of values for the A H the H V interval *is fairly constant* measuring 30 to 55

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msec with an average value of 45 msec

The ability to separate A V nodal and His Purkinje (H P) conduction has enhanced our understanding of normal and abnormal atrioventricular (A V) conduction Abnormal A V conduction may be due to prolongation of P A A H H V, or all three In patients with a P R interval in the upper limits of normal the H V may be abnormally prolonged and when subjected to atrial pacing may reveal latent block of the H P system and thus aid in the differential diagnosis of syncope It should be pointed out however that the H V may be normal and the patient may still have periodic complete distal His block HBE confirmed the fact that when the QRS duration is normal the A V block is usually in the A V node On the other hand in the presence of a prolonged QRS the block may be either in the A H or in the H V regions or in both Second degree block of the Wenckebach type is most often but not always A V nodal in origin while Type II is nearly always due to a block in the H V system Concealed discharge of the bundle of His as a cause of unexpected first or second degree A V block had been proposed from analysis of the surface ECG and conclusively proved with HBE in the human Incomplete penetration of the A V node or bundle of His (concealed conduction) has been repeatedly demonstrated in the human with HBE

HBE clearly confirmed preexcitation of the ventricles in the Wolff Parkinson White (W P W) abnormality In this syndrome the A H is normal and the H V is foreshortened With atrial pacing the A H lengthens normally but the A V conduction by way of the bypass remains unchanged and consequently the H V shortens, the His deflection eventually becoming lost in or actually following ventricular excitation The syndrome of short P R normal QRS and tachycardia has been shown in some instances to be due to foreshortening of the A H interval without any change of the H V period The exact reason for shortening of the A H conduction remains obscure In some of the reported cases the response of the A H interval to pacing is qualitatively the same as in the normal but quantitatively much less pronounced Our understanding of the possible interrelationship of the electrophysiologic manifestations of ventricular preexcitation with anatomic correlates (James Mahaim or Kent bypass) must await further studies The mechanism of antegrade block with preservation of retrograde conduction has been the subject of considerable discussion HBE clearly demonstrates an H potential between the ventricular and atrial electrogram thus strongly supporting unidirectional block with preservation of retrograde V A conduction

Although the major contribution of the His recording has been to our understanding of A V conduction and its various aberrations HBE has provided some help with analysis of ectopic rhythms For example HBE demonstrated clearly that many supraventricular tachycardias are due to reentry within the A V node and that accelerated idioventricular rhythm so frequently seen in acute myocardial infarction is ventricular in origin The ever present problem of differential diagnosis of supraventricular aberrancy and ventricular ectopy can be resolved with HBE recording In the former H precedes V with a normal H V time while in the latter the H deflection is often lost within the ventricular electrogram or if it precedes the local ventricular electrogram it follows the earliest moment of ventricular activation recorded in the multiple surface tracings Rarely ventricular ectopic impulse will activate the bundle of His before giving rise to a QRS and in such a situation an H V shorter than normal will be recorded There is always the possibility however remote that one simply fails to record the H spike during supraventricular rhythm and an erroneous diagnosis of ventricular tachycardia may be entertained

There is little doubt from the foregoing brief review that the HBE has and will continue to contribute to our understanding of arrhythmias and that this avenue of investigation should be pursued by those studying mechanisms of arrhythmias and who are thus equipped for routine HBE On the other hand the utility of HBE in everyday routine care of patients with heart disease is much less secure and in fact is yet to be defined

Irrespective of the invasive nature [illegible] procedure the techn[illegible] and [illegible]mentation require [illegible]

the HBE in the management of the patient will hinge on two factors namely (1) evidence that HBE offers considerable advantage over a carefully analyzed surface ECG correlated with the total clinical picture and equally important (2) our ultimate ability to utilize fully the information obtained with the HBE in the actual care of the patient

At present we are unable to benefit fully from the information inherent in the HBE because complementary parallel clinical facts are not available The following two examples will serve to illustrate this point

The recognition from the HBE that a given supraventricular tachycardia is re entrant in origin rather than automatic will have little effect on the therapy of the arrhythmia until such time that drugs specific for one or the other of the two mechanisms becomes available Similarly recognition that a prolonged H V time is the cause of the prolonged P R interval can be helpful only if the long term prognosis of the H V delay is known

Because of the instrumentation and technique involved in recording His bundle activity the surface ECG will remain the method of choice or perhaps the only method for diagnosis of cardiac arrhythmias available to the vast majority of physicians In fact in emergent situations the lack of HBE should not even raise doubts in the physician s mind as to whether or not proper treatment will be administered The availability of cardioversion a *nonspecific therapeutic intervention* makes it possible after a careful consideration of the total clinical picture to treat the occasional patient with an undiagnosed life threatening arrhythmia without the necessity of having to identify the exact mechanism or site of origin of the arrhythmia However such a nonspecific therapeutic approach to arrhythmias may not always be possible nor desirable For example patients with arrhythmias suspected to be due to a ventricular aneurysm and considered for aneurysmectomy must have the arrhythmia properly diagnosed In such an instance the HBE may prove to be essential and the patient can be referred to a laboratory designed for such an investigation In elective situations in which the patients can benefit from HBE referral for such studies may be desirable

Records of the last 40 patients who have undergone HBE in our institution were reviewed for contribution of this technique to the management of these patients The results from each study were analyzed to determine the potential benefit of HBE to the clinical care of given individuals In only five instances did the HBE prove to be of significant help by providing information not available after analysis of the surface ECG In four cases it aided in the differential diagnosis of ventricular and supraventricular arrhythmia with aberrancy and in one case it identified distal His block in a patient with syncope

HBE has confirmed a number of concepts which evolved from elegant analysis of surface cardiograms It has generated some new knowledge and will continue to enhance our understanding of arrhythmias To date however its contribution to the management of patients with heart disease has been limited This is due not only to (1) the fact that much of the clinically needed information can be obtained from the surface ECG but also in some measure to (2) deficiencies in our knowledge of the basic mechanisms specific therapy and prognosis of various arrhythmias This information if and when available will make the data derived from HBE clinically more useful However until such parallel information does become available the HBE will remain of limited value as a clinical tool

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Clinical communications

Stress electrocardiography in the evaluation of aortocoronary bypass surgery

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The aortocoronary vein bypass operation has pre-empted other myocardial revascularization techniques because of the directness of approach and the high rate of symptomatic improvement.[1-9] Moreover, functional improvement has been documented in terms of significantly increased myocardial blood flow[3,5,8,10-13] and improved ventricular performance.[14-18]

Despite early symptomatic and functional improvement, it is still not clear whether saphenous vein grafts will remain patent over longer periods of time and offset the relentless progression of coronary arteriosclerosis. Furthermore, the psychological effect of surgery is large in patients with angina pectoris, and any revascularization operation has been shown to decrease symptoms in a significant number of cases. For these reasons, objective and easily repeatable methods of evaluation are required to determine if myocardial ischemia is reduced after aortocoronary bypass.

Stress electrocardiography is a practical, non-invasive, safe, and reproducible procedure which has been shown previously to correlate closely with the angiographic results of myocardial revascularization.[19] This report describes evaluation of saphenous vein aortocoronary bypass by standardized pre- and postoperative hypoxemia and graded exercise electrocardiography. In this study, the results of stress electrocardiography are correlated with the symptomatic response and angiographic evidence of graft patency.

Methods

Patients. Details of the clinical material are given in Tables I to III. Forty-six patients having saphenous vein aortocoronary bypass surgery between July, 1970 and January, 1972 were studied.

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Table I Clinical data and stress ECG results

	Those having postoperative angiography		All patients
	One or both grafts open	No open graft	
Number of patients	34	7	45
Male	32	5	41
Female	2	2	4
Age (yr) range (average)	38-61 (50)	42 55 (46)	38 61 (50)
Angina pectoris			
Duration (yr) range (average)	1 13 (5)	0 5 10 (4)	0 5 18 (5)
Functional Class 2	3	0	3
3	29	6	38
4	?	1	4
Prior myocardial infarction	24	5	29
Time since infarction (yr) range (average)	0 5 13 (4)	1 8 (3)	0 5 13 (4)
Preoperative stress ECG range (average)			
Final Sa_{O_2} (%)	66 89 (77)	67 90 (77)	66 90 (77)
Maximum work (kpm/min)	100-1 000 (388)	200-750 (314)	100-1 000 (380)
Maximum heart rate	88 150 (109)	94 141 (110)	88 150 (109)
Postoperative stress ECG range (average)			
Final Sa_{O_2} (%)	67 90 (77)	67 88 (79)	67 90 (78)
Maximum work (kpm/min)	100-800 (515)	150-800 (379)	100 800 (503)
Maximum heart rate	100-150 (127)	100-143 (118)	100-165 (126)
Difference from preoperative average (significance)			
Hypoxemia (% Sa_{O_2})	0 (NS)	+2 (NS)	+1 (NS)
Maximum work (kpm/min)	+127 ($p < 0.01$)	+65 (NS)	+123 ($p < 0.001$)
Maximum heart rate	+18 ($p < 0.001$)	+8 (NS)	+17 ($p < 0.001$)
Time of postoperative (range [average])			
Stress ECG	3 14 (6)	3 11 (6)	3 14 (6)
Angiography	1 12 (5)	3 6 (4)	1 12 (5)

prospectively There was one operative death this report describes the results in the 45 survivors All 45 had pre and post operative stress electrocardiograms and preoperative coronary arteriography 41 had postoperative coronary arteriograms All patients were Functional Class 3 or 4 (New York Heart Association) except for three who were Functional Class 2 All had chronic disabling angina pectoris and none had hypertension left ventricular hypertrophy congestive heart failure atrial fibrillation or were taking digitalis glycosides Twenty nine patients had prior myocardial infarction Postoperative stress electrocardiography was done between 3 and 14 months averaging 6 months after surgery In most cases it was performed the day before postoperative arteriography so that both the patient and the investigators were unaware of the status of the graft The ages ranged from 38 to 61 years averaging 51 years There were 41 men and 4 women

Surgery Twenty six patients had single saphenous vein bypass grafts In 14 cases the graft was implanted to the right coronary artery (RCA) in 12 others it was implanted to the left anterior descending coronary artery (LAD) One patient had triple grafts Eighteen patients had double grafts Of the 19 with two or more grafts 17 had grafts to both the RCA and LAD and two had grafts to both the LAD and circumflex artery

Clinical evaluation A standardized ques

Table II. Stress ECG and angiographic findings in patients with aortocoronary bypass grafts

Patient	Age sex	Preoperative resting ECG	Preoperative coronary arteriography			Postoperative angiography			
						Time (mo.)	Coronary changes from preoperative	Location and condition of graft	
			RC†	LAD	C			Open	Closed
GROUP I									
1 L M	46 M	AMI	40	100	0	4	None	LAD	
2 H B	61 M	N	100*	100*	0				
3 L D	50 M	Ischemia	100*	100	80	4	None	LAD RC	C
4 C W	60 M	IMI	100	100*	90*	1	None	LAD	C
5 A D	60 M	N	100*	80	50	9	Collat. to RC	LAD	RC
6 D I	38 M	N	90*	50*	0	12	None	LAD RC	
7 I M	51 M	Ischemia	0	95	100*	5	None	LAD C	
8 S G	48 M	IMI	100	80*	50	4	None	LAD	
9 T W	61 M	N	100*	80*	0				
10 H I	52 M	AMI	50*	100*	40	6	Occl. proximal RC	RC	LAD
11 W M	45 M	AMI	75*	95	50	9	None	LAD RC	
12 W M	39 M	AMI IMI	100*	90*	0	5	None	LAD RC	
13 T M	54 M	IMI	100*	100*	90	4	None	LAD RC	
14 T W	51 M	N	100*	70*	50	4	None	LAD LC	
		Mean							
		Standard error of mean							
		Significance (p)							
GROUP II									
1 I K	51 M	IMI	95*	40	0	1	None	RC	
2 T W	52 M	IMI	100*	100	0	5	None	RC	
3 D I	43 M	N	80*	0	0	1	None	RC	
4 C M	50 M	IVCD	90*	50*	90*	7	Occl. C	LAD RC	
5 M I	59 M	N	70*	0	90	5	Occl. C	RC	
6 C B	42 M	N	0	100	0	5	None	LAD	
7 W C	58 M	IVCD	90*	50	75	9	Occl. C RC	RC	
8 C W	51 M	Ischemia	100*	70	50				
9 L C	41 M	IMI	100*	80*	40	6	None	LAD RC	
10 C W	61 M	N	100*	75*	0	4	90% stenosis LAD	LAD	
		Mean							
		Standard error of mean							
		Significance (p)							

*Grafted artery.

†Abbreviations: RC = right coronary; LAD = left anterior descending; C = circumflex; N = normal; AMI = anterior myocardial infarction; NS = not significant.

tionnaire was completed each time the patient was seen quantitating the activity level, frequency of angina pectoris, and the consumption of nitroglycerin tablets. The clinical result was classified as *excellent* when the patient was able to return to work and/or had no angina pectoris. Patients with a *good* clinical result were able to more than double their physical activity or had less than half the preoperative frequency of angina and use of nitroglycerin tablets, or both. A *fair* result was characterized by postoperative increase in activity up to twice the preoperative level or a third as much angina or nitroglycerin usage.

Angiography. Selective coronary, left ventricular, and aortic (graft) angiography was done by the percutaneous transfemoral technique of Judkins[20] using 35 mm. cineangiography and sequential cut films. The extent of disease was expressed as the per cent narrowing of the lumen of each vessel.

Pos or neg	Max hypoxemia (% Sa_{O_2})	Pos or neg	Max work (kpm/min)	Max heart rate	Pos or neg	Max hypoxemia (% Sa_{O_2})	Pos or neg	Max work (kpm/min)	Max heart rate	Clinical improvement
Preoperative stress ECG test: Hypoxemia		Exercise			Postoperative stress ECG test: Hypoxemia		Exercise			
+	0	—	400	108	—	77	—	800	150	Excellent
+	83	+	400	100	—	83	—	600	110	Excellent
—	83	+	400	115	—	80	—	600	120	Excellent
+	85	—	600	97	—	85	—	800	150	Excellent
+	80	+	300	94	—	ι0	—	300	135	Excellent
+	75	—	350	136	—	78	—	350	136	Good
+	66	+	400	115	—	67	—	600	142	Good
+	80	+	400	115	—	83	—	600	136	Fair
+	78	+	400	120	—	81	—	800	165	Excellent
+	ι8	—	400	120	—	74	—	600	137	Excellent
+	78	+	200	100	—	73	—	600	115	Excellent
+	78	+	600	111	—	72	—	600	136	Excellent
+	89	+	200	130	—	75	—	600	140	Excellent
+	81	+	400	95	—	80	—	400	105	Good
	79		389	111		77		589	134	
	1 6		32	3 6		1 5		43	4 6	
						NS		<0 001	<0 001	
—	74	—	200	88	—	73	—	600	125	Good
—	68	—	400	107	—	79	—	600	120	Excellent
—	73	—	400	120	—	73	—	600	150	Excellent
—	80	—	400	111	—	81	—	200	100	Good
—	78	—	400	100	—	68	—	600	140	Good
—	68	—	400	95	—	ι0	—	800	136	Excellent
—	72	—	800	105	—	74	—	400	100	Good
—	ι6	—	500	100	—	81	—	700	120	Good
—	87	—	300	107	—	8?	—	800	150	Excellent
—	84	—	200	84	—	82	—	400	107	Excellent
	76		400	102		76		570	125	
	2 1		57	3 6		1 8		63	6 3	
						NS		<0 05	<0 005	

IMI = [illegible] myocardial infarction IVCD = [illegible] del y C llat = ll c r l Oc l = oc l Max = maximum

Stress electrocardiography Patients were studied in the postabsorptive state and no one was taking digitalis at this time or for the two weeks preceding the test In the hypoxemia test patients inhaled a gas mixture of 10 per cent oxygen and 90 per cent nitrogen and the level of hypoxemia was monitored constantly by an earpiece oximeter (Waters) calibrated against Van Slyke arterial oxygen determinations The test was terminated if chest pain occurred if at least 0 5 mm segmental ST depression appeared in the electrocardiogram (ECG) or if the arterial oxygen saturation fell below 70 per cent The maximum duration of hypoxemia was 20 minutes

Graded supine exercise was performed by pedaling a bicycle ergometer (Elema Shonander) in the method standardized in this laboratory [19] The first level of exercise was 100 to 200 kpm per minute this was increased by increments of 100 to 200 kpm per minute until at least 1 0 mm segmental ST depression occurred in the

Table III Stress ECG and angiographic findings in patients with aortocoronary bypass grafts

Patient	Age sex	Preoperative resting ECG	Preoperative coronary arteriography			Postoperative angiography			
						Time (mo)	Coronary changes from preoperative	Location and cond... of graft	
			RC†	LAD	C			Open	Closed
GROUP III									
1 I H	50 I	N	90*	90*	0	1	95% occl LAD less collat	LAD RC	
2 H B	42 M	N	0	100*	0	6	None		LAD
3 H G	42 M	N	40	100*	0	3	None		LAD
4 G M	55 M	IMI	100*	50	0	2	None		RC
5 R C	38 M	IMI AMI	100	100	50	1	None	LAD	
6 R N	53 M	IMI	90	50*	100	5	Occl OM	LAD	
7 R R	47 I	IMI	100	50	50	4	None		RC
8 J H	58 M	IMI	100	50	80	6	70% steno in LAD distal to graft	LAD	
9 H H	39 M	N	0	80*	0	6	None	LAD	
10 H S	43 M	IMI	100*	100	100	3	None		LAD RC
11 R D	49 M	N	100	80*	0	6	None		LAD
12 F H	61 I	N	100*	100	60	2	None	RC	
13 J C	47 F	N	100*	80	90	5	None		LC
14 W L	45 M	IVCD	100*	100*	90	5	95% steno in RC	LAD RC	
15 W D	49 M	N	100*	0	0	4	None	RC	
16 M J	56 M	N	0	90*	0	3	None	LAD	
17 O P	54 M	N	100*	50	0				
18 I D	58 M	AMI	100*	90*	100	6	None	LAD	LC
		Mean							
		Standard error of mean							
		Significance (p)							
GROUP IV									
1 K N	56 M	N	90*	95	0	4	Occl RC	RC	
2 V B	59 M	N	80*	30	95	3	Occl RC C collat to C	RC	
3 A M	46 M	AMI	65*	100*	90	4	None	LAD RC	

*Grafted artery

†Abbreviations RC = right coronary LAD = left anterior descending C = circumflex OM = obtuse marginal N = normal AMI = a[illegible] clusion Max = maximum NS = not significant

ECG or chest pain dyspnea or fatigue terminated the exercise All patients exercised at a given level for 3 minutes and rested for 3 minutes between exercise periods

A standard 12 lead ECG was obtained from each patient prior to stress Special skin electrodes were attached to the extremities and six chest positions and the ECG was obtained by a Hewlett Packard ECG (Sanborn Series 350) 4 channel photographic recorder at a paper speed of 50 mm per second A switching network made it possible to register a complete 12 lead ECG in 10 to 15 seconds Any selected group of 4 leads was displayed continuously on a Hewlett Packard 4 channel oscilloscope (Sanborn Model 569A) and a cardiotachometer (Parks Electronics Laboratory) coupled to the electrocardiograph provided continuous indication of the heart rate The gain of the electrocardiograph was adjusted for 1 0 cm per millivolt The ECG was recorded whenever changes occurred during or at the end of a period of hypoxemia and exercise

Twenty one of the 45 surviving patients had a normal preoperative rest[illegible] ECG

Preoperative stress ECG test					Postoperative stress ECG test					
Hypoxemia		Exercise			Hypoxemia		Exercise			Clinical improvement
Pos or neg	Max hypoxemia (% Sa_{O_2})	Pos or neg	Max work (kpm/min)	Max heart rate	Pos or neg	Max hypoxemia (% Sa_{O_2})	Pos or neg	Max work (kpm/min)	Max heart rate	
		+	100	107			+	100	108	Good
—	67	+	750	141	+	75	—	800	143	Excellent
+	78	+	200	115	+	78	+	400	125	None
+	77	+	200	94	+	84	+	300	115	Good
+	80	+	150	100	—	90	+	150	105	Good
+	84	+	200	115	+	79	+	400	120	Good
+	90	+	200	100	+	85	+	200	100	Good
+	73	+	200	97	—	78	+	400	107	Good
—	76	+	1 000	150	—	80	+	400	125	Good
+	73	+	200	105	+	67	+	400	135	Fair
+	70	+	400	100	+	74	+	400	105	Good
+	88	+	200	100	+	78	—	200	100	Good
+	84	+	250	117	+	88	+	150	100	Good
+	75	+	300	110	+	79	—	400	115	Excellent
—	73	+	500	120	—	84	+	300	120	Fair
+	79	+	200	100	+	74	+	600	143	Excellent
+	73	+	400	125	+	79	+	400	145	Good
+	72	+	200	107	—	74	+	400	125	Excellent
	77		314	111		79		372	119	
	1 6		56	4		1 4		45	3 7	
						NS		NS	NS	
—	75	—	600	111	+	74	—	800	130	Good
—	78	—	1 000	138	+	70	+	800	120	Good
—	75	—	400	100	—	78	+	600	150	Good

myocardial [illegible] IMI = [illegible] myocardial infarct IVCD = [illegible] ventricular conduction delay C [illegible] = collateral Occl = oc[illegible]

(Tables II and III) 18 had records showing prior myocardial infarction but isoelectric ST segments 3 had segmental ST depression in the resting ECG and 3 had intraventricular conduction delays but isoelectric ST segments

The stress test was considered *positive* if either or both hypoxemia and exercise produced significant segmental ST depression (hypoxemia ≧ 0 5 mm exercise ≧ 1 0 mm) Operative ST T alterations usually disappeared by the time of the postoperative study When the resting ECG exhibited ST depression the test was considered positive if there was additional ST segment depression of at least 1 0 mm It is noteworthy that in all instances of positive stress tests so defined the patients experienced typical angina pectoris

Grouping for analysis The entire group of 45 patients surviving surgery was analyzed with respect to the symptomatic result patency of the saphenous vein graft(s) and pre and postoperative stress electrocardiography and coronary arteriography In addition the group was subdivided according to the stress electrocardiographic result in *Group I* (14 pa

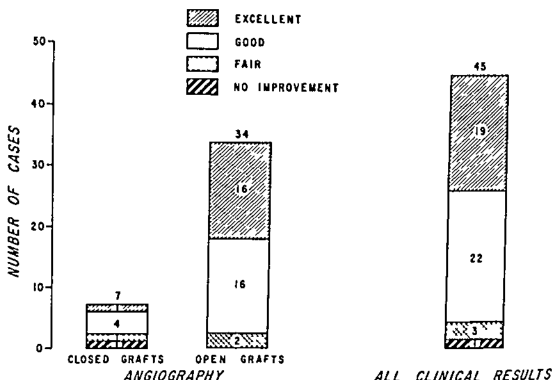


Fig. 1. Correlation of the clinical and angiographic results of aortocoronary saphenous vein bypass graft

tients) the stress ECG was positive preoperatively and became negative postoperatively; in *Group II* (10 patients) both the pre- and postoperative stress ECG's were negative; in *Group III* (18 patients) the stress ECG was positive preoperatively and remained so after surgery; in *Group IV* (3 patients) the stress ECG was negative preoperatively and became positive after surgery. These subgroups were examined with respect to graft patency, the distribution and evolution of obstructing coronary disease, and the maximum work and heart rates achieved before and after surgery. Each patient served as his own control. The significance of results was analyzed using the Student's *t* test.

Results

Clinical results. Fig. 1 shows the clinical results of all aortocoronary vein bypass operations. Of the 34 patients with one or more documented open grafts, 16 had an excellent result, 16 a good result, and two a fair result. In this group, 32 (94 per cent) had significant symptomatic improvement.

In one of the seven patients with closed grafts there was an excellent symptomatic result, in four a good result, in one a fair result, and in one no improvement. Thus, five of seven patients had significant clinical improvement even though the saphenous bypass grafts were closed.

Of the entire group of 45 patients (including four not having postoperative angiography), 19 had excellent results, 22 had good results, there were three fair results, and one had no improvement. Therefore, 41 patients (91 per cent) had excellent or good symptomatic improvement.

Angiography. Angiographic findings are given in Tables II and III. As a whole, the group of 45 had significant occlusive disease of two or more coronary arteries in 31 instances. In 14 cases all significant stenoses were bypassed; in 31 cases residual stenoses could not be bypassed.

In Group I (stress ECG positive preoperatively, negative postoperatively) there was significant coronary disease (i.e., over 50 per cent stenosis) in at least two vessels in 11 of the 14 cases; thirteen of the 14 had double bypass grafts, and significant residual disease in another vessel was not bypassed in four instances. In Group II (stress ECG negative before and after surgery) seven of the 10 had significant disease in two or more coronary arteries; there were seven single grafts, and in four instances significant narrowing of other vessels could not be bypassed. Of the 18 patients in Group III (stress ECG positive

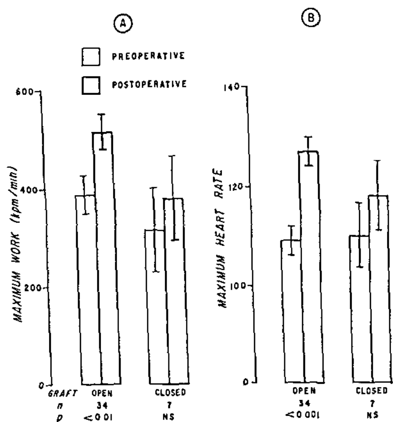
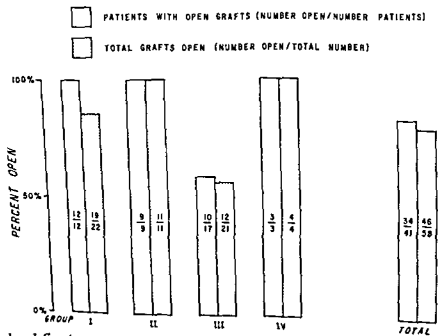


Fig 2 A and B Correlation of aortocoronary bypass graft patency with maximum work (A) and heart rate (B) achieved before and after aortocoronary bypass (the bars delimit one standard deviation of the mean)



Fi 3 Correl t on of aortocoronary bypass graft patency with stress ECG result sub roups

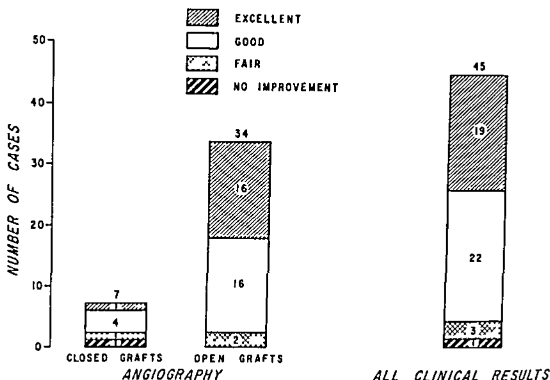


Fig. 1. Correlation of the clinical and angiographic results of aortocoronary saphenous vein bypass grafts.

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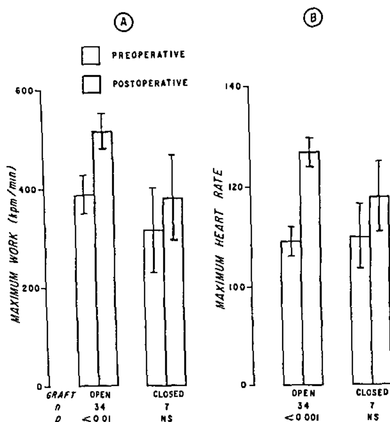


Fig 2 *A* and *B* Correlation of aortocoronary bypass graft patency with maximum work (*A*) and heart rate (*B*) achieved before and after aortocoronary bypass (the bars delimit one standard deviation of the mean)

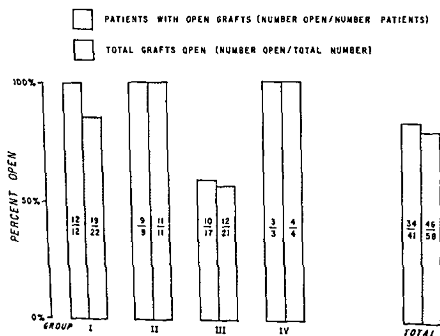


Fig 3 Correlation of aortocoronary bypass graft patency with stress ECG result subgroups

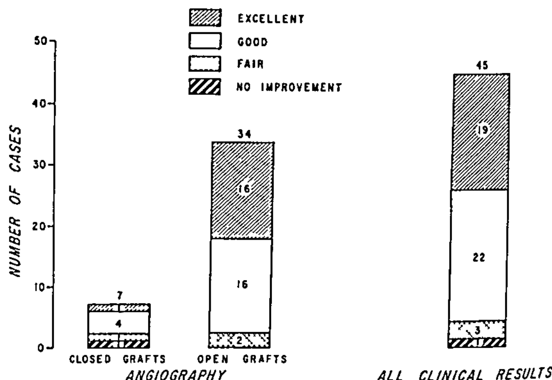


Fig. 1. Correlation of the clinical and angiographic results of aortocoronary saphenous vein bypass graft.

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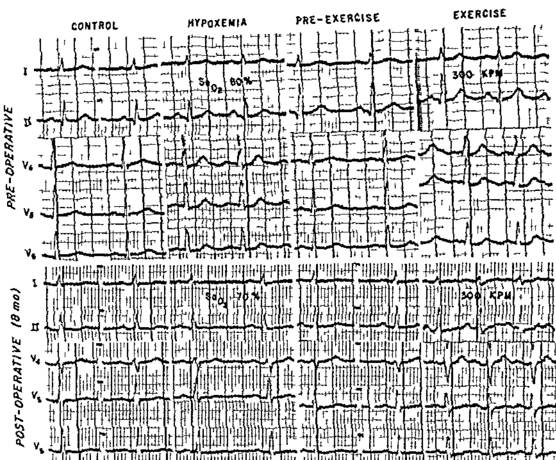


Fig 5 Stre FCG of patient 5 (A D) Group I The preoperative ECG (*upper panel*) shows segmental ST de pres ion mo t marked in V and V with hypoxemia Postoperatively (*lower panel*) there is no significant segmental ST depre ion even at greater hypoxemia

imum work was 379 ± 87 kpm per minute (21 per cent increase $p =$ NS) The mean maximum heart rate achieved by this group preoperatively was 110 ± 6 com pared to the postoperative mean maximum rate of 118 ± 7 (7 per cent increase $p =$ NS) (Fig 2)

Of the 34 patients with one or more grafts open (Table I Fig 1) 22 had posi tive stress ECG tests before surgery and 13 were po itive afterwards (59 per cent) The preoperative mean maximum work performed by this group was 388 ± 38 kpm per minute and the postoperative mean maximum work was 515 ± 35 kpm per minute (33 per cent increase $p < 0.01$) The mean maximum heart rate achieved preoperatively was 109 ± ? compared to the postoperative mean maximum rate of 127 ± 3 (17 per cent increase $p < 0.001$) (Fig 2)

All patients were stressed by the same degree of hypoxemia both pre and post operatively

In general when one stress test was posi tive so was the other In about 10 per cent of instances there was a dichotomy pre operatively the hypoxemia test was posi tive four times when the exercise test was negative and the exercise test was positive four times when the hypoxemia test was negative postoperatively the hypoxemia test was po itive four times when the exer cise te t was negative and the exercise test was positive six times when the hypoxemia test was negative

The stress electrocardiographic results are more meaningful when the entire group

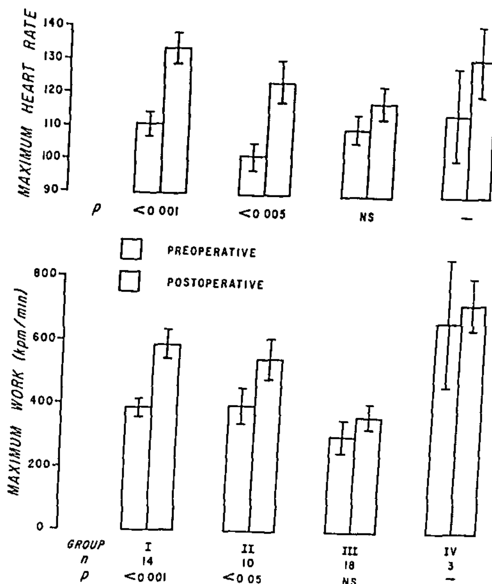


Fig. 4. Relationship between stress ECG result subgroup and maximum work (*lower panel*) and heart rate (*upper panel*) achieved before and after aortocoronary bypass (the bars delimit one standard deviation of the mean).

before and after surgery); significant disease of two or more major coronary arteries was present in 10 cases. 15 of the 18 had single bypass grafts and significant residual disease of other vessels was not bypassed in 10 instances. Of the three patients in Group IV (stress ECG negative preoperatively, positive postoperatively) two had single grafts and one had double grafts; in all cases there was significant disease of at least two vessels and residual stenosis was not bypassed in all instances.

Postoperative angiography was done in 41 patients between one and 12 months after surgery, averaging five months (Tables I, II, and III). One or more grafts were open in 34 (83 per cent) and seven patients had no open graft. Of all the saphenous bypass grafts, 46 of 58 (79 per cent) were patent (Fig. 3).

Eight patients had interval occlusion or progression of proximal stenosis in the grafted coronary artery. Five had interval occlusion of other non grafted vessels and one developed significant intercoronary collaterals after surgery. In three instances there was more than 50 per cent stenosis in the coronary artery distal to the bypass graft.

Stress electrocardiography. The seven patients with closed grafts (Table I, Fig. 1) had positive stress ECG results both before and after surgery. The preoperative mean maximum work performed was 314 ± 64 (standard error of the mean) kpm per minute and the postoperative mean max-

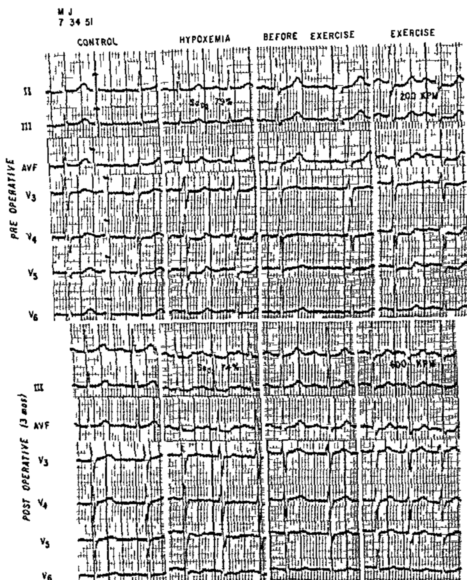


Fig 7 Stress ECG of patient 16 (M J) Group III The preoperative hypoxemia and exercise tests (*upper panel*) are highly positive Postoperatively (*lower panel*) the hypoxemia test is equally positive the exercise test less so both at greater level of hypoxemia and exercise

and II (53 per cent) had objective evidence of improvement in terms of negative post operative stress electrocardiograms and the achievement of significantly more work and greater heart rates after surgery All of these patients who had postoperative angiography (21) were found to have at least one open bypass graft Groups III and IV (47 per cent) were objectively either no better or were worse after surgery had positive postoperative stress electrocardiograms and were unable to achieve significantly greater work or heart rates after surgery Only 13 of the 20 patients (65 per cent) in these groups had patent grafts

Discussion

The evaluation of any myocardial revascularization technique is complicated by the symptomatic variability of the disease and by the influence of a number of interacting variables which tend to obscure



Fig. 6. A through C. Coronary angiograms of patient whose stress ECG is depicted in Fig. 5. There is occlusion of the left anterior descending coronary (A, preoperative, and B, postoperative) successfully bypassed in C.

of 45 patients is subdivided on the basis of the preoperative test result and the change (if any) which occurred after surgery. In Group I the stress ECG was positive before surgery and became negative postoperatively in this group of 14 patients (31 per cent). Twelve of these patients had postoperative angiograms showing patent grafts in all cases. There was a total of 22 grafts in these 14 patients and 19 grafts were open (Fig. 3). Most patients in Group I were able to perform significantly more work and achieve significantly greater heart rates postoperatively (Fig. 4). Preoperatively the group accomplished a mean maximum work level of 389 ± 32 kpm per minute and postoperatively 589 ± 43 kmp per minute (51 per cent increase, $p < 0.001$). Before surgery they achieved a mean maximum heart rate of 111 ± 4; after surgery 134 ± 5 (21 per cent increase, $p < 0.001$). Figs. 5 and 6 illustrate pre- and postoperative angiograms and stress electrocardiograms in a patient of Group I.

In Group II the stress ECG was negative both before and after surgery (10 patients, 22 per cent). Postoperative angiography in nine of these patients showed that all bypass grafts were patent (Fig. 3). Most of the patients in this group performed significantly more work and reached a significantly greater heart rate postoperatively (Fig. 4). Preoperatively the group reached a mean maximum work level of 400 ± 57 kpm per minute, postoperatively 570 ± 63 kpm per minute (43 per cent increase, $p < 0.05$). The mean maximum heart rate increased from 102 ± 4 preoperatively to 125 ± 6 postoperatively (23 per cent increase, $p < 0.005$).

The 18 patients in Group III (40 per cent of the total) had positive stress electrocardiograms both before and after surgery. Seventeen of these had postoperative angiography, showing that 10 patients had one or more grafts open and that 12 of the 21 total grafts in this group were open (Fig. 3). Most patients in this group were not able to generate significantly more work or greater heart rate after surgery (Fig. 4). Preoperatively the group reached a mean maximum work level of 314 ± 36 kpm per minute and postoperatively 372 ± 45 kpm per minute (18 per cent increase, $p =$ NS). The pre- and postoperative maximum heart rates achieved were 111 ± 4 and 119 ± 4, respectively (7 per cent increase, $p =$ NS). Figs. 7 and 8 illustrate pre- and postoperative angiograms and stress electrocardiograms in a patient of Group III.

Group IV comprised three of the 45 patients (7 per cent) whose stress ECG was negative preoperatively and positive after surgery. All three had open bypass grafts (Fig. 3). As a group they achieved higher work levels and heart rates both before and after surgery (Fig. 4), but further comparisons with the other groups are invalidated by the small number.

In summary, the 24 patients in Groups I

residual non bypassed coronary obstruction

Patients in Group II with postoperative negative stress ECG tests and increased heart rates and work production illustrated the need to quantitate the work and heart rates achieved during exercise since some patients with bona fide coronary disease had negative stress electrocardiography or the tests were aborted by chest pain before discriminating ECG changes occurred Although most of the patients in this group had single grafts there was a relatively low incidence of residual non bypassed coronary disease and like Group I all patients had one or more patent grafts Taken together Groups I and II showed good correlation between negative postoperative stress ECG tests and improved coronary circulation resulting from at least one patent aortocoronary graft

The patients in Groups III and IV had positive postoperative stress ECG tests and collectively were unable to generate significantly greater heart rates or work in comparison to the levels achieved preoperatively The persistently abnormal stress results in Group III correlated with the relatively low incidence of open grafts (6 per cent) and the larger number of coronary obstructions which were not bypassed Group IV patients reversed their originally negative stress ECG tests becoming positive postoperatively although they were able to do more work and achieve greater heart rates than before surgery All of the patients in Group IV had significant disease of other vessels and two of the three had postoperative coronary occlusions

It seems clear from these simple and noninvasive studies that stress electrocardiography and quantitation of the heart rate and work achieved by exercise provide a relatively accurate objective assessment of the results of aortocoronary bypass surgery Although over 90 per cent of patients were improved symptomatically and nearly 80 per cent of the vein bypass grafts were patent at the time of postoperative angiography only 53 per cent were objectively improved

The predictive value of stress electrocardiography was especially high The graft patency rate was 90 to 100 per cent when (1) the stress ECG was positive preoperatively and reversed postoperatively or (2) when the stress ECG was negative both before and after surgery and the patients could achieve significantly greater work and heart rates postoperatively On the other hand when the stress test remained positive or became so after surgery there was only about 65 per cent probability that one or more grafts were open and a high probability of significant residual coronary obstruction Moreover in all instances in which there was no open graft after surgery the postoperative stress ECG was positive and there was no significant increase in heart rate and work over that achieved by preoperative exercise

Summary

Forty five patients having saphenous vein aortocoronary bypass surgery were studied prospectively by pre and postoperative hypoxemia and graded exercise electrocardiography The stress electrocardiographic results were correlated with the degree of symptomatic relief and the angiographic evidence of graft patency and the distribution and evolution of coronary occlusive disease

Forty one of the total group of 45 patients (91 per cent) and 32 of 34 (94 per cent) with one or more documented open grafts had excellent or good symptomatic improvement Incongruously five of seven patients with closed grafts also had significant clinical improvement

Functional improvement was documented in 53 per cent of patients after aortocoronary bypass surgery in terms of postoperative reversal of the preoperatively positive stress ECG or persistance of a negative stress ECG together with the achievement of significantly greater mean maximum exercise and heart rate All of these patients had one or more patent saphenous vein bypass grafts Forty seven per cent of the patients failed to display objective evidence of improvement postoperatively the stress ECG either remained positive or became so and collectively the group was unable to significantly increase the mean maximum exercise level or heart rate in comparison to that achieved before surgery Only 65 per cent of these



Fig. 8. *A* through *D*. Coronary angiograms of patient whose stress ECG is depicted in Fig. 7. The right coronary is normal (*A*) and there is 90 per cent stenosis of the left anterior descending (*B*), successfully bypassed in (*C*) and (*D*).

whether myocardial ischemia is in fact diminished after surgery. Indeed, pain relief after operation may be at least in some part the result of the period of enforced bed rest during pre- and postoperative care, operative infarction of a pain-producing zone of ischemic myocardium, and postoperative physical and emotional conditioning. Although postoperative angiography verifies the patency of saphenous vein aortocoronary bypass grafts, it provides inadequate quantitation of the degree of functional improvement which results from the balance between increased coronary flow provided by the bypass graft and residual coronary obstruction which could not be bypassed. Moreover, it may not be feasible or desirable to do postoperative angiography in all cases. For these reasons standardized hypoxemia and exercise electrocardiography was employed as an objective measurement of the functional result of aortocoronary bypass surgery. The reproducibility of hypoxemia[19] and exercise[19-21, 2] electrocardiography has been established as long as exercise is graded from levels below the threshold for a positive response is maintained for at least three minute periods, and the patients are not undergoing physical training.[3]

The majority of patients in this study had significant symptomatic improvement. Over 90 per cent had excellent or good clinical results, and about 80 per cent of all grafts were patent when examined angiographically five or six months after surgery. These results are quite similar to those reported by others.[3-11] Incongruously, most of the patients with occluded grafts also were improved symptomatically after surgery.

Stress electrocardiography provided more discriminating evaluation of the functional results of surgery. The patients with closed aortocoronary bypass grafts exhibited persistently positive stress electrocardiography and as a group failed to achieve significantly greater heart rates and exercise when tested postoperatively. On the other hand, the mean maximum heart rate and work achieved as a group by those with one or more grafts open increased significantly after surgery, although stress electrocardiography was positive in almost half of the patients after surgery. Normalization of the exercise ECG and increase in the heart rate–blood pressure product have also been observed by Amsterdam and colleagues[24] and by Bergman and associates in the majority of patients examined early after aortocoronary saphenous vein bypass.

In this study the complicated interrelationship between saphenous vein bypass graft patency and residual coronary obstruction was best expressed in relation to the difference, if any, between preoperative and postoperative stress electrocardiography. The patients in Group I reversed their originally positive preoperative stress ECG, becoming negative after surgery, and generally achieved significantly greater heart rates and exercise postoperatively. Although all of the patients had one or more grafts open, this group also had the greatest number of double bypass grafts and the least

reproducit ility and follow up re ults Circulation 43 and 44(Suppl II) 76 1971
23 I edwood D R Rosing D R and Ep tein S F Circulatory and symptomatic effects of phy ical training in patients with coronary artery di ea e and angina pectoris N Engl J Med 286 959 1972
24 Amsterdam E A Iben A Hurley E J Mansour E Hughes J L Salel A F Zelis R and Mason D T Saphenous vein bypass graft for refractory angina pectoris physiologic evidence for enhanced blood flow to the ischemic myocardium Am J Cardiol 26 623 1970
25 Bergman S A Urschel H C Jr and Blomqvist G Pre and postoperative exercise testing in patients undergoing direct myocardial revascularization Circulation 43 and 44 (Suppl II) 141 1971

subjects had one or more patent bypass grafts.

Stress electrocardiography and quantitation of the maximum work and heart rate achieved by exercise provide accurate assessments of the relief of myocardial ischemia produced by myocardial revascularization. In this study, when the postoperative stress ECG was negative and the patient was able to achieve significantly greater exercise and heart rate, the probability of patency of one or more bypass grafts was virtually certain. On the other hand, when the postoperative stress ECG was *positive* and little or no increase in exercise and heart rate was possible, there was high probability of graft occlusion or significant residual coronary disease.

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in identifying slurs in the waveform but that the identification of a notch was much less subjective and was consistently identified by several observers. Therefore we decided to re-examine our initial group of subjects to determine whether appropriate new diagnostic criteria could be developed. We were successful in developing satisfactory new criteria. 966 subjects who received routine health examinations at the University of Pennsylvania Health Evaluation Center were studied by wide band recording of the electrocardiogram using our new criteria.

Material and methods

1 Original subjects. Two groups which had been studied prior to 1966 were selected for further analysis. Group A consisted of the 100 normal controls[9] who were healthy male employees of the Provident Mutual Life Insurance Company. This group received annual health maintenance examinations. High frequency records from these subjects have been obtained at intervals of two to three years since 1950 and were followed up to 1966; records made prior to 1956 were still available and were used in this study. The ages at entry were 38 to 65 with a mean age of 51 years. Myocardial infarctions[9] occurred in three members of this group in the interval 1955 to 1966; all the others have remained free from heart disease. Since 1966 24 new male subjects were added to our group. Two of the new entrants developed coronary artery disease with myocardial infarction; their records will be discussed separately.

Group B consisted of 76 ambulatory subjects who had recovered very satisfactorily from a well documented myocardial infarction[9]; their ages were 43 to 75 years with a mean age of 56 years. Six of these subjects were female.

2 Health Evaluation Center studies. Since 196[illegible] a series of high frequency electrocardiograms have been obtained on 966 ambulatory male subjects at the Health Evaluation Center at the Hospital of the University of Pennsylvania. These patients were studied by the usual clinical methods including chest x-ray, conventional electrocardiogram, blood chemistries, hemoglobin, white blood count and other non-invasive techniques as deemed appropriate. The ages were 35 to 72 years with a mean age of 57 years. Eight hundred seventy five (875) of these subjects were classified as normal; 24 had documented histories of myocardial infarction; 12 had a diagnosis of angina pectoris; 35 had systolic blood pressure greater than 160 mm. Hg and diastolic blood pressure higher than 100 mm. Hg; 20 had a cholesterol level of 300 mg. per cent or higher.

Methods

Records from Group "A" (100 subjects) plus Group "B" (76 subjects) were made by photographing the face of a cathode ray oscilloscope on 5 inch wide rapidly moving (350 mm. per second) photographic paper.[5] Records from the Health Evaluation Center group (966 people) plus 24 new subjects from the insurance company were made by photographing the face of a cathode ray oscilloscope with continuously moving 16 mm. film.[20] Examples of high frequency notching utilizing this technique are shown in Figs. 1 and 2. Excluding major changes of directions of QRS such as peaks of the R and nadirs of the Q and S waves, slurs and notches are defined as changes of the slope of QRS. Slurs are departures from the smooth slope without change of signs whereas notches are changes both of slope and sign. Since 1969 records have been made with a Linc 8 computer. The output of this computer is displayed on an oscilloscope and three consecutive complexes are photographed with a polaroid camera.[21] Comparison of records obtained using both the moving film and the computer has indicated that the configuration of the waveform is essentially identical. The frequency response of all three systems exceeded a range flat from 0.15 to 1000 Hz. Standard scalar limb and precordial leads were used in all wide band studies.

Results

Analysis of original 176 subjects (Groups A and B). All notches and slurs in the three largest limb leads and the six precordial V leads in these 176 subjects are tabulated in Table I. Table II is based on identical data but omits all information from Leads V_1, V_2 and V_3. Notches only appearing in the three largest limb leads and in V_4, V_5 and V_6 are tabulated in Table III. It can

Wide band recording of the electrocardiogram and coronary heart disease

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Wide band recording of the electrocardiogram utilizing an expanded time scale and greater amplitude[1,2] than the conventional method is a useful tool because it increases the detection rate of myocardial disease. Our previous studies have demonstrated that one of the chief values of this method is its unique capability of recording high frequency notches and slurs which are much more common in the QRS complex of patients with clinical and preclinical coronary heart disease than in apparently healthy subjects.[3-9] These high frequency notches and slurs are not revealed by the conventional electrocardiogram even when its frequency response is raised to 100 Hz. Other investigators have published studies utilizing high frequency electrocardiography which have confirmed these findings of increased notching in heart disease. This work includes studies of patients with coronary artery disease,[10-17] patients with cardiomyopathies,[18] biventricular hypertrophy,[1,17] and rheumatic heart disease.[19] Of these investigators, Burch and co workers[10,11] and Selvester and co workers[13] used the spatial vectorcardiogram. Franke and Braunstein[12] used power spectrum analysis. Flowers, Horan and colleagues[15-17] made extensive studies using three orthogonal leads in both coronary heart disease and biventricular hypertrophy. Reynolds and co workers[13] employed a modified spatial vectorcardiogram.

Our earlier studies indicated that people without heart disease could be distinguished from subjects with coronary heart disease by enumerating the total number of notches and slurs in the three largest limb leads and the six precordial V leads.[9] A similar method was initiated in a program involving persons seen at the Health Evaluation Center at the Hospital of the University of Pennsylvania to expand these studies to a large group of subjects. As this study progressed we found a considerable overlap in the notch plus slur count in V_1, V_2 and V_3 between the so called normal group, which by noninvasive clinical techniques revealed no evidence of coronary heart disease, and a group of subjects having well documented coronary heart disease. It had also become apparent to us that there was some ambiguity

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Table I. Combined number high frequency notches and slurs in nine leads

Notches and slurs	Normal subjects	Abnormal subjects	Notches and slurs	Normal subjects	Abnormal subjects
0	2	0	21	0	4
1	0	0	22	0	10
2	2	0	23	0	2
3	4	0	24	0	3
4	5	0	25	0	5
5	11	0	26	0	2
6	9	0	27	0	0
7	9	0	28	0	2
8	13	0	29	0	4
9	13	0	30	0	1
10	11	2	31	0	6
11	9	1	32	0	4
12	6	4	33	0	2
13	2	4	34	0	0
14	1	2	35	0	1
15	1	2	36	0	0
16	2	3	37	0	0
17	0	0	38	0	0
18	0	4	39	0	1
19	0	1	40	0	0
20	0	5	41	0	1
			Totals	100	76

notches plus slurs, six leads counting notches plus slurs, and six leads counting notches alone) can differentiate normals from abnormals ($P < 0.001$). For screening purposes the last procedure was chosen, employing the three largest limb leads and V₁, V₄, and V₆ counting notches only. This decision, validated by the foregoing statistical analysis, was justified by the fewer number of leads and events to be counted and by simpler incorporation into a computerized system to be reported later.

Health Evaluation Center Data. Results for the Health Evaluation Center subjects are summarized in Table IV. On clinical grounds, 8[illegible] subjects were classified as normal. Of the clinically normal group, 89 per cent had three notches or less and 11 per cent had a notch count of four or more. Approximately 300 of these subjects had two or more high frequency electrocardiograms at yearly intervals for four years. None of these exhibited any significant serial change except for one subject who developed myocardial infarction and is included in the infarction group (Fig. 3).

There were 24 patients with well documented histories of myocardial infarction and all but two had abnormal conventional electrocardiograms. As shown in Table IV, 79 per cent of the 24 subjects had an abnormal number of notches. Repeated high frequency records at intervals of a year or more showed no serial changes. There were 12 subjects with a diagnosis of angina pectoris; of these seven had an abnormal number of notches. The electrocardiogram of one of these subjects is seen in Fig. 4. The last two groups are hypertension (160/100 or higher—3? subjects) and hypercholesterolemia (300 mg. per cent or higher—20 subjects). Notching in these two categories was not higher than in the normal group. All members of the group (Table IV) were active and gainfully employed. No one had a history of congestive heart failure. Only three of the 3[illegible] subjects with hypertension had mild to moderate left ventricular hypertrophy. Of the three subjects with left ventricular hypertrophy by conventional electrocardiographic standards, none had excess high frequency notching.

Additional Provident Mutual Life Insurance Company employees. All 24 of these subjects had normal conventional low frequency and high frequency electro

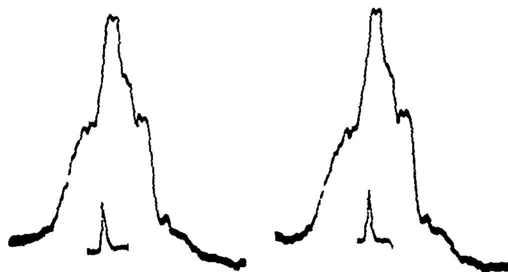


Fig. 1. Two consecutive high frequency complexes (Lead II) with the conventional recording below. There is obvious notching in the large high frequency tracing which cannot be identified in the conventional records below.

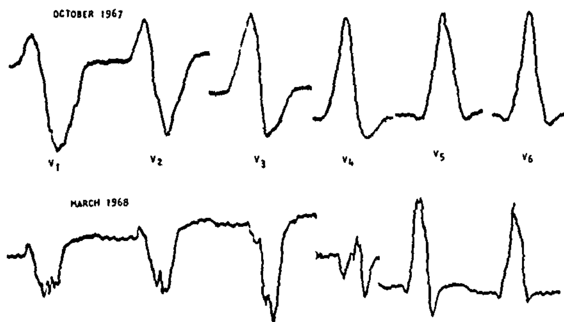


Fig. 2. The upper panel consists of high frequency chest leads made in 1967 prior to infarction. The bottom panel shows high frequency records made from the same precordial sites after infarction. After infarction Lead V_3 consists of a QS complex and V_4 shows obvious low frequency serial change. None of the notching evident in the lower tracing was present in the conventional electrocardiogram of the same date.

be seen in Table I that 94 per cent of normals have 12 or fewer notches and slurs and 91 per cent of those with heart disease have more than 12 notches and slurs. In Table II 89 per cent of subjects without heart disease have six or less notches and slurs whereas 89 per cent of those with heart disease had more than six notches and slurs. Table III contains the number of notches (slurs omitted) in the three largest limb leads and in V_4, V_5, and V_6. Ninety-two per cent of those without heart disease had three notches or less but 93 per cent of subjects with heart disease had more than three notches. Results from Tables I, II, and III were examined statistically. The Median Test[22] confirmed that each of the three procedures (nine leads counting

Table I Combined number high frequency notches and slurs in nine leads

Notches and slurs	Normal subjects	Abnormal subjects	Notches and slurs	Normal subjects	Abnormal subjects
0	2	0	21	0	4
1	0	0	22	0	10
2	1	0	23	0	2
3	4	0	24	0	3
	5	0	25	0	5
5	11	0	26	0	2
6	9	0	27	0	0
7	9	0	28	0	2
8	13	0	29	0	4
9	13	0	30	0	1
10	11	2	31	0	[illegible]
11	9	1	32	0	4
12	6	4	33	0	2
13	2	4	34	0	0
14	1	2	35	0	1
15	1	2	36	0	0
16	2	3	37	0	0
17	0	0	38	0	0
18	0	4	39	0	1
19	0	1	40	0	0
20	0	5	41	0	1
			Total	100	76

notches plus slurs six leads counting notches plus slurs and six leads counting notches alone) can differentiate normals from abnormals ($P < 0.001$). For screening purposes the last procedure was chosen employing the three largest limb leads and V_4, V_5 and V_6 counting notches only. This decision validated by the foregoing statistical analysis was justified by the fewer number of leads and events to be counted and by simpler incorporation into a computerized system to be reported later.

Health Evaluation Center Data Results for the Health Evaluation Center subjects are summarized in Table IV. On clinical grounds 875 subjects were classified as normal. Of this clinically normal group 89 per cent had three notches or less and 11 per cent had a notch count of four or more. Approximately 300 of these subjects had two or more high frequency electrocardiograms at yearly intervals for four years. None of these exhibited any significant serial change except for one subject who developed myocardial infarction and is included in the infarction group (Fig 3).

There were 24 patients with well documented histories of myocardial infarction and all but two had abnormal conventional electrocardiograms. As shown in Table IV 79 per cent of the 24 subjects had an abnormal number of notches. Repeated high frequency records at intervals of a year or more showed no serial changes. There were 12 subjects with a diagnosis of angina pectoris; of these seven had an abnormal number of notches. The electrocardiogram of one of these subjects is seen in Fig 4. The last two groups are hypertension (160/100 or higher—35 subjects) and hypercholesterolemia (300 mg per cent or higher—20 subjects). Notching in these two categories was not higher than in the normal group. All members of the group (Table IV) were active and gainfully employed. No one had a history of congestive heart failure. Only three of the 35 subjects with hypertension had mild to moderate left ventricular hypertrophy. Of the three subjects with left ventricular hypertrophy by conventional electrocardiographic standards none had excess high frequency notching.

Additional Provident Mutual Life Insurance Company employees All 24 of these subjects had normal conventional low frequency and high frequency electro

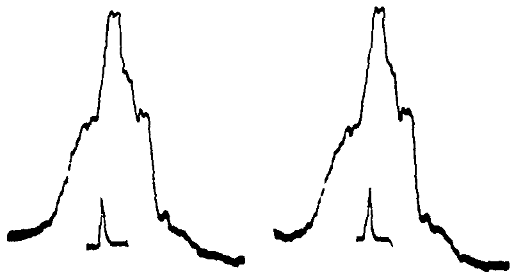


Fig 1 Two consecutive high frequency complexes (Lead II) with the conventional recordings below There is obvious *notching in the large high frequency tracing* which cannot be identified in the conventional records below

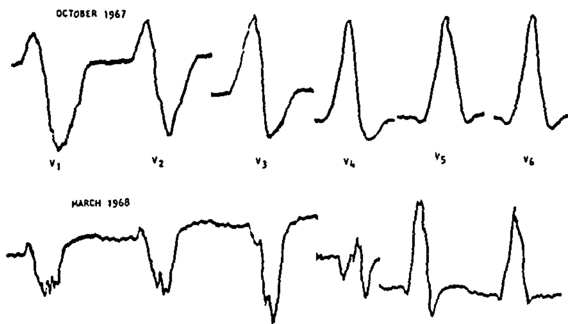


Fig 2 The upper panel consists of high frequency chest leads made in 1967 prior to infarction The bottom panel shows high frequency records made from the same precordial sites after infarction After infarction Lead V_3 consists of a Q S complex and V_4 shows obvious low frequency serial change None of the notching evident in the lower tracing was present in the conventional electrocardiogram of the same date

be seen in Table I that 94 per cent of normals have 12 or fewer notches and slurs and 91 per cent of those with heart disease have more than 12 notches and slurs In Table II 89 per cent of subjects without heart disease have six or less notches and slurs whereas 89 per cent of those with heart disease had more than six notches and slurs Table III contains the number of notches (slurs omitted) in the three largest limb leads and in V_4 V_5 and V_6 Ninety two per cent of those without heart disease had three notches or less but 93 per cent of subjects with heart disease had more than three notches Results from Tables I II and III were examined statistically The Median Test[2] confirmed that each of the three procedures (nine leads counting

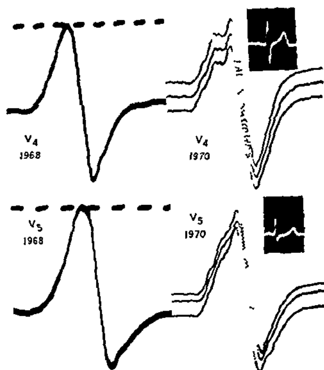


Fig 3 High frequency recording at sites V_4 and V_5 prior to infarction in 1968 and after a well documented episode of myocardial infarction in 1970 The latter records were made by photographing the oscilloscopic display of a Linc 8 computer The conventional 12 lead electrocardiogram in 1970 (V_4 and V_5 inserted) was normal

Table IV Total number of high frequency notches in leads V_4, V_5 and V_6 together with the total number of notches in the three largest limb leads (Health Evaluation Center)

Normal		*Abnormal*			
Number of notches	*Normal*	*Myocardial infarction*	*Angina*	*Hypertension*	*Hyper cholesterolemia*
0	281	1	2	10	7
1	268	1	2	8	4
2	123	2	0	8	5
3	107	1	1	5	3
4	50	2	1	2	0
5	20	1	0	1	0
6	10	2	1	0	0
7	6	3	0	0	1
8	4	1	1	1	0
9	3	1	0	0	0
10 or more	3	9	4	0	0
Totals	875	24	12	35	20

Table II Combined number notches and slurs in three largest limb leads and in V_4, V_5, and V_6

Notches and slurs	Normal subjects	Abnormal subjects	Notches and slurs	Normal subjects	Abnormal subjects
0	6	0	15	0	4
1	11	0	16	0	4
2	18	1	17	0	3
3	17	0	18	0	2
4	12	2	19	0	7
5	16	3	20	0	2
6	9	2	21	0	6
7	3	4	22	0	1
8	6	2	23	0	0
9	1	6	24	0	1
10	1	4	25	0	1
11	0	7	26	0	1
12	0	4	27	0	0
13	0	5	28	0	0
14	0	3	29	0	1
			30	0	0
			Totals	100	76

Table III Notches in three largest limb leads and in V_4, V_5, and V_6

Notches	Normal subjects	Abnormal subjects	Notches	Normal subjects	Abnormal subjects
0	38	1	15	0	5
1	26	2	16	0	2
2	13	1	17	0	2
3	15	1	18	0	1
4	5	3	19	0	2
5	3	5	20	0	0
6	0	5	21	0	1
7	0	7	22	0	0
8	0	5	23	0	1
9	0	3	24	0	0
10	0	3	25	0	0
11	0	5			
12	0	4	Total	100	76
13	0	10			
14	0	7			

cardiograms Twenty two have continued to be normal The other two have exhibited serial changes One subject initially seen in 1966, developed angina pectoris in 1970 At that time his high frequency electrocardiogram exhibited notching in Leads I aVR and V_6 The second subject entered the study in 1965 at the age of 55 years In August 1970, he appeared for routine examination A high frequency electrocardiogram revealed changes not present in 1965 which were most marked in V_4 (Fig 5) Approximately a month later he died suddenly of acute myocardial infarction

Discussion

In 1966 we reported that normal subjects could be separated from subjects with coronary heart disease by counting the total number of notches and slurs in the three largest limb leads and six precordial V leads [9] Using criterion of 12 notches and slurs or less to define the normal group we

1 1 me 86
N mb 3

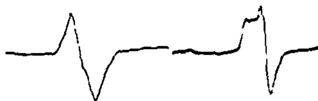


Fig 5 The complex at the left is V_4 recorded in 1965 The distorted and notched complex at the right is V_4 obtained in 1970 One month later the patient died of an acute myocardial infarction

of these hypertensive subjects had left ventricular hypertrophy as noted by conventional electrocardiography with normal heart size judged by routine chest x ray None of these had increased notching

There is evidence that the pathophysiological basis of notching in the electrocardiogram is fragmentation or interruption of the usual smooth path of excitation in the ventricular wall due to patchy necrosis or scarring in the myocardium [4 6] Langner and associates [7] have demonstrated that subepicardial injection of formalin in the intact dog resulted in myocardial lesions and high frequency notching of the QRS complex Flowers and colleagues [16] have shown that high frequency notching and slurring seen ante mortem in the high frequency electrocardiogram in the orthogonal Y and Z leads could be correlated with the site of infarction at post mortem

If fragmentation of excitation due to necrosis or scarring is indeed one of the mechanisms for the genesis of notching then our results in instances of two risk factors hypertension and hypercholesterolemia can be interpreted to indicate that in cases such as these there may not yet be sufficient myocardial alteration to cause excess notching

During the present study we encountered seven subjects with angina pectoris who had excess notching in the high frequency electrocardiogram when the conventional electrocardiogram was normal In an earlier study we reported three cases from our original control group who had excess high frequency notching just prior to development of acute myocardial infarction Two additional cases of this type have been reported here

Heart disease is a principal cause of death in this country A recent study [28] has indicated that the recognition of coronary heart disease in the preclinical stage at the time of a routine health examination is almost totally inadequate in persons who subsequently died of myocardial infarction We have shown that high frequency notching in the electrocardiogram is significantly increased in subjects with known coronary heart disease and in some cases appears de novo just before acute myocardial infarction On the other hand not all patients with coronary artery disease have high frequency notching as in five of our cases with typical angina pectoris and both a normal conventional electrocardiogram and a normal high frequency electrocardiogram

Summary

Wide band high frequency electrocardiography employing an expanded time scale and both greater amplitude and a greater frequency response than conventional electrocardiographs reveals small notches in the QRS complex which are obscured in the conventional electrocardiogram A total of more than three high frequency notches in Leads V_4 V_5 and V_6 plus the notches in the three largest limb leads suggests a high probability of coronary heart disease This criterion is a modification of one we previously reported in that now fewer leads need be examined and slurs are not counted In a control group of 100 normal subjects and 76 subjects with coronary artery disease used to develop this new criterion there were 8 false positives (8 per cent) and 5 false negatives (7 percent) The Health Evaluation Center group provided 966 new subjects who were studied using the high frequency technique 875 were classified as normal 11 per cent had an abnormal number of notches Of 24 patients with

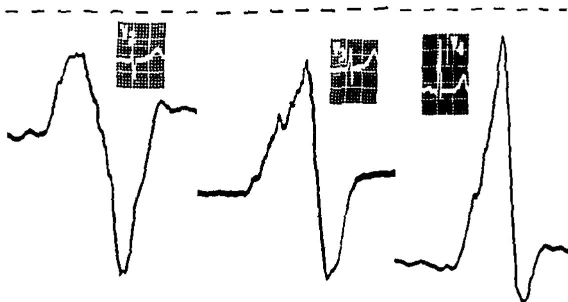


Fig. 4. High frequency electrocardiograms below and conventional electrocardiogram above (Lead V_1, V_2, and V_4) from a patient with angina pectoris and 80 per cent occlusion of two coronary arteries on angiography. Notching in the high frequency tracing is self evident. The *entire 12 lead conventional electrocardiogram was normal.*

observed 6 per cent false positives and 9 per cent false negatives. A restudy of this group of subjects has indicated that adequate separation can be achieved by counting notches alone in V_4, V_5, and V_6 and in the three largest limb leads. The false positive rate then is 8 per cent while the false negative rate is 7 per cent (Table III). As indicated under *Results*, the confidence level for any of these criteria is high ($P < 0.001$). We feel that the new criterion (counting notches alone in 6 leads) is simpler. The elimination of a count of slurs removes some ambiguity when records are read by visual inspection and also facilitates development of computer programs for interpreting high frequency records. Of interest is the observation that there was no increased notching with age over a ten year period except in three cases who developed myocardial infarction.

Although we have found the counting of notches alone adequate as a screening procedure for reading a single high frequency electrocardiogram recorded from the standard limb and precordial V leads, there may be instances when slurs are significant. Flowers, Horan, and colleagues[1, 17] have found slurs as well as notches significant in their studies which used orthogonal X, Y, and Z leads. In a small study of 20 subjects comparing standard precordial V leads with orthogonal X and Z leads, we have found that a given high frequency component appearing as a definite notch in a precordial V lead may appear as a slur in the X or Z lead.[23]

The Health Evaluation Center study has enlarged the over-all number of subjects in the long-term study. This group consists of ambulatory working males who are predominantly normal. The percentage of false positives (11 per cent) is 3 per cent higher than in the group used to develop the present notching criterion. However, follow-up for the Health Evaluation Center group was about 30 per cent compared to 100 per cent for the Provident Mutual Life Insurance Company employees who have been followed for a much longer period of time.

Abnormal subjects from the Health Evaluation Center constitute a small group. The percentage of false negatives in the infarct group (24 cases) was 21 per cent. In a group of twelve subjects with a diagnosis of angina pectoris there were 42 per cent false negatives. In the two high risk groups, hypertension and hypercholesterolemia, no increase in the number of subjects with excess notches o are

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histories of myocardial infarction, 79 per cent showed excess notching Of 12 subjects with angina pectoris 7 showed excess notching Notching in the 35 patients with uncomplicated hypertension and in 20 subjects with hypercholesterolemia was within the normal range Twenty four additional Provident Mutual Life Insurance Company employees were added to our long term study Of these two developed coronary artery disease Both exhibited serial changes in the high frequency electrocardiogram

Wide band electrocardiography using the sum of the notches in the three largest limb leads and the notches in V_4 V and V_6 is a useful adjunct for the detection of coronary heart disease especially when the conventional electrocardiogram is normal

We wish to thank Thomas W Clark M D for his assistance in data collection and Dayle H Stare B A M A for his help with the statistical analysis We also wish to acknowledge the technical assistance of Mrs Freda S Leaver

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struction and the rest had pure valvular stenosis The age range was from one to 47 years with a mean of 16 years Patients with left to right shunts at any level were excluded but small to moderate right to left shunts on the atrial level were accepted Two patients had slight tricuspid regurgitation but none had frank congestive heart failure Thirty three of the patients had ECG and VCG recordings made within one week after the hemodynamic investigation In the other five this interval was about two years but in none of them was there any change in ECG or clinical condition during this period Three subjects had a QRS duration of 0 11 or 0 12 second in these the presence of a conduction defect could not be ruled out None had QRS duration exceeding 0 12 second Subjects with the Turner phenotype were excluded[7]

ECG and VCG Twelve lead ECG s were recorded with Elema Schonander Mingographs of various models all having a high frequency response (linear to 500 Hz) and a high input impedance (exceeding 10 megaohms) VCG s were recorded with the axial lead system[8] by means of silver electrodes and a Sanborn 185B amplifier (input impedance about 100 megaohms) and a 569B Visoscope The skin was rubbed with acetone before electrode attachment Ordinary axis orientation was used Vector loops were photographed in the horizontal right sagittal and frontal projections with special emphasis on the presentation of the initial dots The highest frequency response and a beam interruption interval of 2 5 msec was always used Scalar X Y and Z leads were recorded with an Elema Schonander Mingograph 34 with the characteristics mentioned at paper speeds of both 50 and 250 mm per second

X Y and Z components of each spatial vector were derived through a manual analysis of scalar and planar recordings This process involved in many instances some degree of judgment as to the identification of vectors in different planes the main difficulty being that the dots were not identically timed on different pictures Maxima and minima were derived solely from the scalar tracings since the continuous record allowed better identification of optima situated between dots and the

Table I Data selected for correlation with right ventricular pressure

A Vectorcardiographic data
- X Y and Z of each 10 msec QRS vector up to 80 msec
- X Y and Z of maximal T and ST vector
- QRS maximum and minimum of X Y and Z
- X minima were separated into early (septal) and secondary (later than 20 msec) minima
- Time from QRS onset to each maximum and minimum QRS duration
- QRS rotation in horizontal plane (counterclockwise = 1 figure of 8 = 2 clockwise = 3)
- Maximal spatial QRS vector (MSV)
- Maximal rightward spatial vector (MRSV) Definition 1 = maximal spatial vector pointing to the right of the midline Definition 2 = spatial magnitude of maximum rightward vector (X min)
- Maximal rightward—anteriorly oriented QRS deflection along the 135 to 315 degree axis in horizontal plane (max RA)
- Maximal leftward—posteriorly oriented QRS deflection parallel with the same axis (max LP)
- Arithmetic sum of RA LP deflections for each 10 msec QRS vector (ΣRA LP)

B Electrocardiographic data
- R V_1 S V_1 R aVR R I S I R V_6 S V_6

C Other data
- Age

average of several beats could be used

Hemodynamic data Right heart catheterization was performed in all patients and right ventricular angiography was made in all except those with a right ventricular pressure below 50 mm Hg The peak systolic right ventricular pressure was selected as the single hemodynamic variable of interest This pressure is pathophysiologically and clinically fundamental in this lesion and has previously been shown to be the hemodynamic variable which correlates best with ECG data[2 3]

Right ventricular systolic pressure did often vary somewhat during the investigation The most representative resting pressure was selected by the hemodynamic investigator independently of ECG or VCG data

Data selection For each patient 58 items of VCG and ECG data were selected (Table I) The data were chosen to comprise almost all information present in the QRS complex while ST and T were recorded in less detail The QRS rotation in the horizontal plane was coded as figure-of 8 when even

Prediction of right ventricular systolic pressure in pulmonary stenosis from combined vectorcardiographic data

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Although heart catheterization and angiocardiography have become increasingly precise and safe procedures, it still is and will be an important goal in cardiology to extract as much information as possible from noninvasive techniques. The best such method for the diagnosis of ventricular hypertrophy has been electrocardiography (ECG) in one form or another. Isolated right ventricular pressure overload as seen in pulmonary stenosis with intact ventricular septum is well suited for the testing of further progress in this field. The lesion is hemodynamically simple and the easily obtainable right ventricular peak systolic pressure is commonly accepted as the best index of degree of disease.[1]

The hypothesis underlying most work done with the ECG prediction of hemodynamic data has been that there is a fundamental relationship between the functional load, the degree of anatomical changes induced by this load, and some properties of the electrical forces created within these anatomical structures.[1] One has therefore sought for the components of these forces which give the best prediction of pressure or flow. Generally, three methods are available in the efforts to improve the results obtained with conventional ECG. (1) An orthogonal vectorcardiographic (VCG) system may be substituted for the ECG.[2-5] (2) The dipole model may be changed to a more complex physical model involving multiple dipoles[4] or multipoles.[6] Although the first of these methods recently has been shown to yield promising results, these methods will for a long time remain investigational procedures. (3) The information obtained through ECG or VCG could be used to better advantage through the combination of several measurements.

This report presents the results of our efforts along lines (1) and (3). The axial lead system has been used for VCG measurements and a multiple regression analysis has been made in order to select the best data combination for pressure prediction.

Materials and methods

Patients. Thirty-eight unselected patients with a diagnosis of unoperated pulmonary stenosis with intact ventricular septum were included in the study. Four patients had a pure infundibular stenosis, two had combined valvular and infundibular ob-

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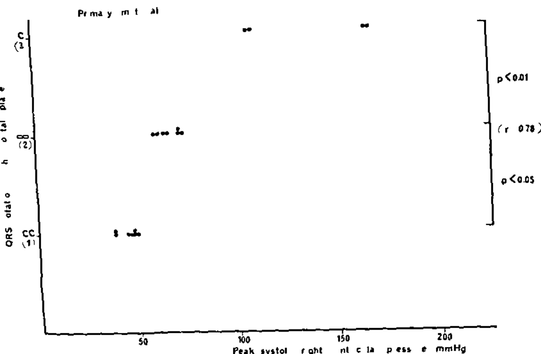


Fig 1 Relationship between direction of QRS inscription in horizontal plane and right ventricular pressure

new equilibrium has had time to be established[11,12] In three cases the time between the pressure measurement and the VCG recording was more than half a year with some clinical or ECG signs of progression The last five patients had small left to right shunts on the ventricular level (below 25 per cent of pulmonary flow) and one of them had in addition an intermittent third degree A V block Thus this material was less homogeneous than the primary one but was nevertheless thought to be useful for the evaluation of the derived formula

Results

Altogether 40 of the 58 independent variables proved to be significantly correlated with right ventricular systolic pressure at the 5 per cent level and 33 of the correlations were significant also on the 1 per cent level The best of these individual correlation coefficients are presented in Table II As seen the best individual predictor was found to be the classical VCG variable of direction of QRS rotation in the horizontal plane The calculation of a correlation coefficient for this variable is however not quite correct since it is not continuously distributed The individual data for QRS rotation pressure relationships are shown in Fig 1

Another closely related and continuously distributed index namely (max RA–max LP) had the same correlation coefficient (0 78) (Fig 2) We have found this measurement to be of some value because the variation around the regression line is smallest in the lower pressure range where the practical importance of an index of severity is greatest For a sample of this size the 95 per cent confidence interval of this correlation coefficient is from 0 61 to 0 88

It should further be noted from Table II that the best conventional ECG variable came out as No 6 and that the second definition of MRSV was somewhat better than the first and more commonly applied definition The new indices based on RA LP relationships were not particularly useful compared with more commonly used variables Time variables did generally yield poorer results than the voltage variables

The multiple stepwise regression calcu

Table II Correlation coefficient between individual ECG and VCG measurements and right ventricular systolic pressure*

No	Variable	r
1	QRS rotation horizontal plane	0 78
2	Max RA	0 74
3	T Z	0 74
4	ST Z	0 74
5	MRSV definition 2	0 73
6	R V_1	0 72
7	S I	0 72
8	Z min	0 71
9	Z 50 msec	−0 71
10	Σ RV I I	0 68
11	MRSV definition 1	0 68
12	X min 2	0 68
13	MSV	0 67
14	Z 60 msec	−0 67
15	Time Z min	0 66
16	Z 40 msec	−0 64
17	T Y	−0 63
18	X 60 msec	−0 61
19	X 70 msec	−0 57
20	R aV_R	0 56
21	Z 70 msec	−0 55
22	Z max	−0 52
23	S V_1	−0 51
24	Max LP	−0 51
25	Y 70 msec	0 50
26	Y 60 msec	0 50
27	ST Y	−0 48
28	Y 80 msec	0 47
29	X 80 msec	0 46
30	X 50 msec	−0 45
31	Z 80 msec	−0 45
32	Y 50 msec	0 44
33	S V_6	0 42

*All correlations are significant ($p < 0.01$ or less) The variables are ranged according to the height of the coefficient

the slightest part of the loop had rotation opposite to the main loop Both of the two possible definitions of the much used maximal rightward spatial vector (MRSV) were included

With increasing right ventricular hypertrophy the QRS loop shifts gradually from a posterior leftward to an anterior rightward position in average approximately around the 315 to 135 degree axis in the horizontal plane An effort was therefore made to quantitate this shift through the measuring of the maximal anterior rightward (AR) and posterior leftward (PL) deflections parallel with this axis The shift of the total QRS loop was quantitated through the derivation of the sum of these deflections for each 10 msec vector

Although the study was not primarily designed to compare ECG and VCG some of the most used ECG measurements for the diagnosis of right ventricular hypertrophy were also selected Age was used as the single non ECG variable

Data treatment The 58 items of data on each patient were entered as independent variables and the peak systolic right ventricular pressure is the dependent variable in a multiple regression computer program (BIMD 09)[9] using a CDC 3600 computer This program is essentially a combined step up and step down procedure[10] starting with the best individual predictor and at each step including the new predictor which gives the greatest reduction in the rest variance in terms of having the largest F value Predictors which lose their significance during the procedure are discarded F values of 5 0 were chosen as limits for both entering and removal of variables corresponding to a minimum significance level of about 5 per cent Through this process the formula of the order

$$\text{Pressure} = a + b_1x_1 + b_2x_2 + \quad + b\,x$$

which gives the best possible prediction of pressure in this material is computed

In addition to the Cartesian coordinates a computer run was also made with derived spherical coordinates (spatial magnitude, azimuth and elevation) Because of the slight skewness in the distribution of right ventricular pressure in the material logarithmic transformations of the variables were also tested

Secondary material Any regression equation derived from a limited sample may give poorer results in a secondary sample Therefore a secondary material consisting of 19 unselected patients with pulmonary stenosis as their main lesion was sampled in order to test the results Five patients satisfied the inclusion criteria of the primary material Six patients had been operated on for their lesion more than one year previously and a new hemodynamic investigation had been made Previous studies indicate that ECG pressure correlations are unchanged in such patients if a

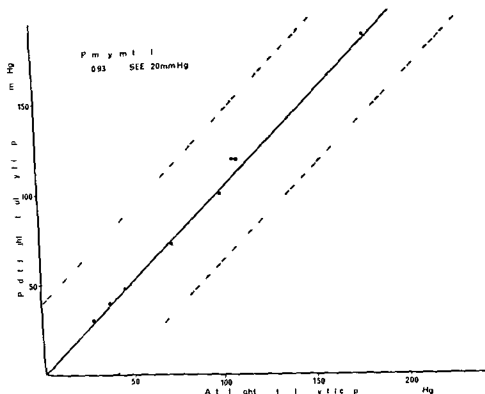


Fig 3 Relationship between actual right ventricular systolic pressure and the pressure computed by means of the equation described in the text

selected except for the exclusion of subjects with the Turner phenotype This material is the first of its type in which this group has been explicitly excluded This would be expected to result in improved correlations and has definitely done so in this material Patients with Turner phenotype and normal chromosomes constitute about seven per cent of the population with pulmonary stenosis [7]

The age range in this material is large compared to many previously reported the mean age is also comparatively high

ECG VCG technique Both the recording technique and the manual derivation of instantaneous vectors contain possible errors The quality of the data could probably have been somewhat improved through the use of computer wave recognition and data sampling [13] The greater error in the measurement of instantaneous vectors than of maxima and minima may possibly be partly responsible for the comparatively low diagnostic performance of the former This work may therefore be regarded as representative of what can be accomplished through manual ECG and VCG measurements which in most centers will remain the only method for many years

Data selection An almost infinite number of VCG variables and combinations may be derived and analyzed The possibility that other indices could improve the results is always there but it seems unlikely that the improvement would be great

Because the number of ECG variables tested was so small the results have limited value in the comparison of the optimal diagnostic performance of ECG vs VCG It is possible that individual or combined ECG variables could be found in this material that might give as good results as the VCG variables

It is also possible that the results could be improved by taking other hemodynamic parameters into consideration for instance left ventricular systolic pressure

Data treatment The choice of the coefficient of correlation and the standard error of estimate as the sole criterion of diagnostic performance in this and pre

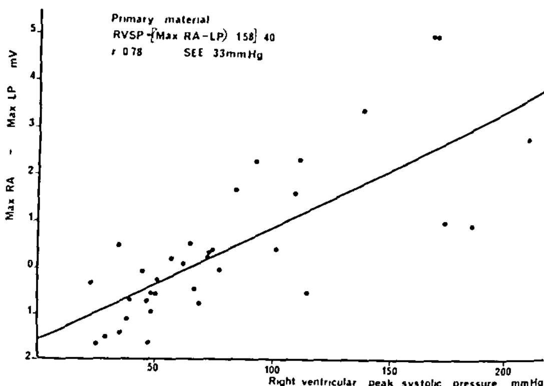


Fig. 2. Relationship between max RA–max LP index and right ventricular systolic pressure. The scatter around the regression line is least in the 50 to 80 mm Hg region.

lation proceeded through five steps; at each step a new variable was introduced into the equation. The following formula was derived:

$$RVSP = -57.6 + 15.4\ ST\ Z + 21.3\ Y\ max + 62.4\ Y\ min + 35\ QRS\ rot_H + 1.4\ age$$

Through the use of this formula the correlation coefficient between actual and predicted pressure increased from 0.78 to 0.93, the 95 per cent confidence interval of the latter being from 0.87 to 0.96. The standard error of the pressure estimate (SEE) was reduced from 33 to 20 mm Hg (Fig. 3).

All the coefficients in the equation had standard errors of less than one third of their absolute values.

The use of spherical coordinates in the regression analysis did not improve the results. Again horizontal plane QRS rotation was selected as the first step, the next being the spatial magnitude of ST and maximal T vector. The individual vectors' spatial magnitude correlated much better than the angles with pressure. Logarithmic transformations gave much poorer results.

An effort to combine the seven ECG variables and age into a formula was unsuccessful, since it produced only two significant steps.

As would be expected from the less rigid patient selection, most of the individual predictors showed poorer results when applied to the secondary material (QRS rot H r = 0.69, R V_1 r = 0.68). Others showed better results than in the primary material (MRSV r = 0.91, max RA r = 0.89, ST r = 0.79). The derived equation gave a somewhat—but not much—poorer prediction than in the primary material with a correlation coefficient of 0.88 (95 per cent confidence interval 0.71 to 0.95) (Fig. 4). Two patients in the secondary material fell outside the ±2 SEE of the primary material, one above and one below the regression line. The one above had a ventricular septal defect with a variable left to right shunt which may have added significantly to the right ventricular load and the one below had A V block during the catheterization (heart rate 44 per minute) and the pressure measured may therefore have been higher than usual. Thus the deviations may to some extent be explained by the different sample selection.

Discussion

Patient selection. This is an important aspect in this kind of work since the exclusion of a few atypical patients may falsely improve the results considerably. The present material is in this regard un

the square root of the number of patients. This requirement is satisfied in the present work. With increased sample size the multiple regression method may be applied with greater benefit and confidence. Even then the value of the formula derived can be properly tested only on future samples as attempted here.

Results. Individual correlation coefficients. With the above mentioned sources of error in mind, some of the results will be compared with previous ones.

In this study single VCG variables were found to have a small superiority over single ECG variables. This is in contrast to Cambon and co-workers[2] who found a much larger benefit of Frank VCG and also in some contrast to Borun and Sapin[5] (cube and Frank VCG) who found no benefit at all. A moderate diagnostic improvement resulting from the substitution of VCG for ECG was also found by Witham and associates[3] (Helm system) and Holt and associates[4] (Frank system). No conclusion can be drawn regarding the superiority of one VCG system or another in this type of diagnosis from these studies. The present work is, however, the first of this kind in which the axial lead system has been used and the results are well comparable with those obtained with other orthogonal systems.

The degree of correlation found here for several simple ECG and VCG indices (RV_1, S I, MRSV) is in good accordance with several previous reports.[2-4, 17-20] The best individual correlations have been published by Witham and associates[3] but they were using rather uncommon VCG variables and the material was small.

The high diagnostic performance of the QRS rotation in the horizontal plane that was found is at some variance with previous results with other lead systems. For the cube system this is probably caused by too high sensitivity to slight increments in right ventricular pressure.[19-21] Clockwise rotation of the loop seems to occur at about the same pressure level in the Frank and the axial lead systems[3] but the transition from counterclockwise to clockwise rotation is possibly more abrupt with the Frank system.[2] This is, however, partly dependent on the exact definition of loop rotation applied.

Voltage maxima and minima were found to be definitely more firmly related to right ventricular pressure than the time intervals used to reach these optima (Table II). This is contrary to the proposition recently made by Arntzenius[2] to use such time intervals in the diagnosis of ventricular hypertrophy. In addition his method may be difficult to apply because the deflection points may have no precise definition in abnormal loop rotations. Both the time interval method and the use of single vector magnitudes in the diagnosis of hypertrophy are based on the partly invalid hypothesis that single instantaneous vectors may be generated in only one part of the heart.

Recent work on the VCG diagnosis of right ventricular hypertrophy has been dominated by the use of the MRSV as an index. The results from the primary material (Table II) indicate that this dominant role is not altogether justified. On the other hand, MRSV was the best predictor in the smaller secondary material. The new index based on anterior rightward loop dislocation did not prove to be particularly useful.

In recent VCG studies either Cartesian or spherical coordinates have been used; this divergence has been one of the many in this field which has decreased the applicability of the results. This study indicates that no information is lost by using the less sophisticated Cartesian coordinates.

Benefit from multiple regression analysis. In the present study a statistically significant and potentially practically important improvement of pressure VCG correlations was provided through the combination of several VCG data. The derived equation is simple and rapid to apply; in addition to scalar VCG leads, one needs only a photograph of the horizontal plane QRS loop.

Two groups of workers have previously to some degree applied the principle of predictor combination for estimating right ventricular pressure in pulmonary stenosis. Witham and associates[3] selected eight promising variables for a multiple regression analysis, thereby restricting the factors which could be taken into account. They obtained a formula which included seven primary variables, a large number considering the small sample of 21 patients. When comparing with the best individual variable only a small improvement was found.

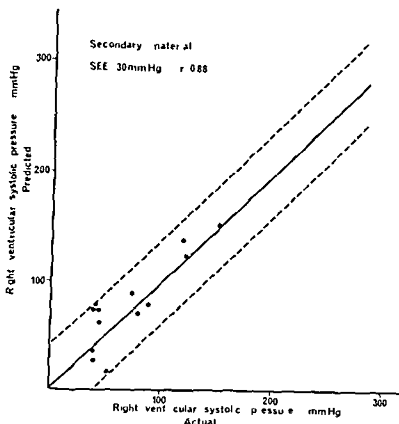


Fig. 4. Relationship between actual and equation predicted systolic right ventricular pressure in the secondary material.

vious works[2,5] may be disputed. This choice implies that all pressure regions are treated as equally important while the practical importance of the correlations is greater in the 50 to 100 mm Hg region. The derived equation is actually somewhat better in the upper pressure region.

Linear regression analysis does in a strict sense require a normal distribution of data. This is not completely satisfied in this material, but better than in several previous ones.[2,4]

The most important limitation in this and most of the previous studies[2,4] is the small sample size. This causes the confidence intervals of the coefficients to become so large that reliable conclusions concerning the relative diagnostic value of different variables and combinations can often not be drawn. This factor has often not been properly considered and may explain most if not all of the differences in results for instance regarding the superiority of ECG or VCG.[14] This applies also to most of the differences found in this study. The comparison of correlation coefficients and standard errors of estimate from different materials is still more misleading.

As demonstrated by the large number of significant individual predictors the situation dealt with is statistically characterized by a large number of measurements which are highly correlated with right ventricular pressure and which also have a high degree of intercorrelation. The problem in the multiple regression analysis is to select the variable which at each step gives most additional knowledge. Beyond the first step this is usually not the variable with the best individual performance. The variable that is selected is also dependent on very small differences in F values. A new computation from a slightly different sample may lead to the selection of an entirely different set of variables but probably providing about the same amount of information as the first set. Thus too much weight should not be placed upon the selection of variables that have appeared in the final equation.

Uncritical application of results from multiple regression analysis of a sample to the population may lead to serious errors.[15] Gamboa, Klingeman and Pipberger[16] advocate that the number of variables included in a multivariate formula should not exceed

catheterized patients This situation is somewhat different since previous recordings from the same patient may serve as control data and thereby increase the diagnostic accuracy Changes from time to time in VCG pressure relationship may be assumed to occur parallel with the regression line (3) The effect of surgery may similarly be evaluated thus contributing to the decision of whether a postoperative catheterization should be made

In patients with right ventricular hypertrophy caused by various other kinds of congenital and acquired heart disease the pressure VCG relationship will usually be different particularly when a flow load is added to a pressure load However if the VCG is interpreted not in terms of pressure but of anatomy the results may possibly have value also in other conditions

Summary

In 38 patients with isolated unoperated pulmonary stenosis a systematic search was made for optimal VCG criteria for the prediction of peak systolic right ventricular pressure Fifty VCG measurements seven ECG measurements and age of each patient were entered into a stepwise multiple regression computer program

The best individual predictors were found to be the QRS loop rotation in the horizontal plane and the closely related QRS *dislocation along the 135 to 315 degree* horizontal plane axis ($r = 0.78$) Five VCG criteria were better than the best ECG criterion ($R\ V_1$ $r = 0.72$) Thirty three of the 58 variables showed significant correlations with the pressure ($p < 0.01$) Since the confidence intervals are large with this sample size and degree of correlation conclusions regarding the superiority of one predictor vs another should be drawn with great care

The *multivariate equation* selected by the computer involved four VCG variables and age this improved the correlation co*efficient to 0.93* This improvement from data combination is larger than in previous studies probably because all variables were given equal opportunity to enter the equation

The results were tested on a secondary sample of 19 patients with pulmonary stenosis as their main cardiac lesion Although this sample was less homogeneous the formula derived pressure estimates remained reasonably good ($r = 0.86$) The study suggests that the diagnostic power of ECG and VCG could be increased through the proper combination of easily *obtainable measurements*

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with reduction of standard error of pressure estimate from 19 to 15 mm Hg

Borun and Sapin[5] studied a much larger sample of 90 patients with Frank and cube VCG and conventional ECG They found the best single variable to be R V_1 ($r = 0.79$, SEE = 19 mm Hg) Adding one or two variables (S_x or $R_x/[R_x + S_x]$) improved the correlation coefficient to 0 83 and 0 84 They apparently did not use a computer program to select the optimal data combination

Thus the main difference between these two reports and the present is that in the latter all 58 variables have been given an equal opportunity of being included in the equation This may probably explain most of the larger benefit from data combination

Secondary material As discussed any correlation, selected because it is good will tend to decrease when a second sample is analyzed Multiple regression equations are particularly vulnerable in this respect The presently supplied secondary material was not ideally suited because of the heterogeneity but it was the only sample available The great changes in correlation for several of the individual predictors illustrate the sample dependency of these results The persisting good correlation between actual and formula predicted pressure, with most of the data falling within ±2 SEE of the regression line indicate that the formula really reflects properties of the pulmonary stenosis population as such and that it may be of practical help in future work with VCG in this group Although two individual variables yielded results about as good as the formula in the secondary material the formula is definitely better when both materials are considered and showed a better sample stability

General discussion Even if one assumes a complete correspondence between physiology anatomy, and ECG the correlations between these entities must be restricted by the repeat variabilities of the measurements involved The repeat variability of ECG and VCG data is largely known[23] but data on the reliability of right ventricular pressure measurements are as far as we know not available However even during the same investigation the pressure may vary by several millimeters of mercury Therefore, it seems doubtful if SEE of such correlations can be reduced to below 10 mm Hg

Another source of persisting variation around the regression line is the factor of obstructive infundibular pulmonary stenosis In this condition the resting pressure may be low but it may increase steeply at small levels of exercise ECG and VCG may correctly, show changes compatible with advanced right ventricular hypertrophy and are therefore a better indicator of degree of disease than an isolated pressure measurement

Different left ventricular pressures with consequent differences in left ventricular electrical forces will probably also decrease the correlations this factor may partly have been responsible for bringing the age into the equation

The main conclusion which may be drawn from the present work is that there is a substantial benefit to be gained from combining VCG data in the diagnosis of right ventricular hypertrophy After the formula has been developed all that is required is conventional VCG measurements and a short time for calculation This time is well spent in this group of patients where important decisions regarding prognosis catheterization and operation are to be made It is possible that the results achieved in this way may be as dependable as those obtained by the use of complex physical models involving a large number of measurements and complicated computer calculations[4] Before spending too much energy on these interesting lines of research one should ascertain that more easily obtainable data are used optimally

The practical importance of the results lies in the improved ability to estimate the degree of pulmonary stenosis in cases where this diagnosis is fairly certain The three typical situations of use are as follows (1) In the previously uncatheterized patient the regression equations may be helpful in establishing if heart catheterization is indicated and if operation should be planned at an early stage The practical value of the pressure estimate in this situation is restricted by the fact that catheterization is also made in order to confirm the diagnosis and to exclude the presence of additional defects (2) The method may be used to evaluate progression in previously

catheterized patients This situation is somewhat different since previous recordings from the same patient may serve as control data and thereby increase the diagnostic accuracy Changes from time to time in VCG pressure relationship may be assumed to occur parallel with the regression line (3) The effect of surgery may similarly be evaluated thus contributing to the decision of whether a postoperative catheterization should be made

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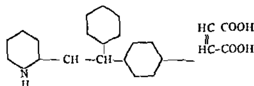
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The action of perhexiline maleate in patients with angina

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Perhexiline maleate is a new antianginal drug found to be effective in recent double-blind trials in America and the United Kingdom. In a majority of the patients there was a substantial reduction in anginal attacks and in glyceryl trinitrate consumption.[1-5]

Perhexiline maleate closely resembles a predecessor hexadiline which was reported on by Rowe and associates.[6] Its chemical name is 2-(2,2-dicyclohexylethyl) piperidine maleate; it has the following structural formula:



In animals the drug induces systemic arterial vasodilatation, increased coronary blood flow, reduced heart rate, and increased pulmonary compliance.[7, 8]

We report here a double-blind clinical study of perhexiline undertaken to assess its effect on heart rate and blood pressure at rest, on graded exercise, and at the point of angina. Respiratory function and daily walking were also measured.

Patients and methods

Eleven men with typical angina pectoris of frequent occurrence were invited to the study. Their ages ranged from 45 to 67 with a mean of 53. Length of history ranged from six months to 12 years with a mean of five years. Five had normal resting electrocardiograms (ECG), two showed horizontal S-T segment depression, one an old anterior and one an old posterior myocardial infarct. One showed complete left and the last complete right bundle branch block. None of the ECG's altered during the trial. There was no recent change in the pattern of angina pectoris in any patient and no recent myocardial infarction. At the time of study none showed left ventricular failure.

The study consisted of a two week control period during which all tablets except glyceryl trinitrate were discontinued, followed by a four week trial period. The trial was double blind, the patient taking either perhexiline maleate (200 mg.) at 9 A.M. and 6 P.M. or placebo tablets identical in appearance and taste, each for two weeks by random selection during the trial period. Each patient attended for exercise tests on a bicycle ergometer on three occasions at fortnightly intervals starting at the end of the control period.

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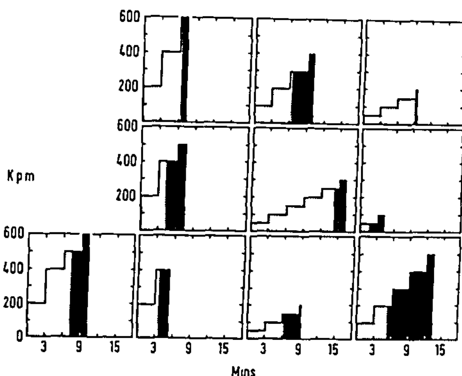


Fig. 1. Performance on drug vs placebo. Hatched sections represent exercise tolerance on placebo. Dark sections represent increase in exercise tolerance on perhexiline. End point in each case is angina.

On the test days the patient was instructed not to smoke and not to drink tea or coffee after 10 A.M. He had a light lunch at 12:30 P.M. and attended the Cardiac Department in the afternoon. Patients were asked to avoid taking glyceryl trinitrate on test days; if the drug was taken, the tests were abandoned.

On arrival the patient rested in an examination room for ten minutes. He was then examined, the pulse rate over one minute was measured and also the blood pressure by sphygmomanometry. The patient walked through to the study room where an ECG was recorded. Remaining supine he was attached to a bicycle ergometer (Elema Schonander type AM 368). Lead V_5 was monitored by oscillosope to which a recorder was attached. Five minutes later pulse rate and blood pressure were again recorded.

The patient then cycled at 60 revolutions per minute in the supine position, the load increasing every three minutes. At each load blood pressure was recorded after two minutes and the ECG after two and a half minutes. The heart rate at each load was measured as the mean of 20 beats. At the first visit the loading was adjusted until angina developed in less than 15 minutes.

At each subsequent visit the patient cycled to the point of angina three times and stopped five seconds later, the end point heart rate being measured during this interval. Three loading regimes were used: 50 k.p.m. increasing by 50 k.p.m. increments; 100 k.p.m. increasing by 100 k.p.m. increments; and 200 k.p.m. increasing to 400, 500 and 600 k.p.m.

Room temperature was kept between 73 and 78° F. It did not vary by more than 3° F for any patient. Forced vital capacity and forced expiratory volume were recorded on a Vitalograph. The patient was instructed in the use of a pedometer and the number of miles walked during the trial was recorded.

Results

One of the 11 patients discontinued his tablets, subsequently found to be perhexiline, after four days of the second period of the trial because of dizziness. The results analyzed are those from the other ten patients.

When the code was broken after the study and all measurements had been completed it was found that six patients had taken perhexiline first and four placebo. Exercise tolerance was greater in

Table I Work performance on placebo and perhexiline

Patient	Placebo (k p m × time)	Perhexiline (k p m × time)	Percentage increase on perhexiline
1	2 030	2 630	30
2	1 120	2 200	96
3	910	1 026	13
4	1 147	2 183	90
5	2 033	2 563	26
6	99	272	175
7	2 500	4 190	68
8	947	1 620	71
9	472	943	100
10	807	3 733	363
Mean	1 206	2 136	77

all cases on perhexiline than on placebo ($p < 0.01$) The increase in the total amount of work performed (product of work load and time) varied from 13 to 362 per cent with a mean of 77 per cent (Fig 1 Table I) Two patients who had perhexiline before placebo had an exercise tolerance on placebo less than after the control period

In the first test of each study day (Table II) resting heart rates on perhexiline were significantly lower than on placebo but on placebo they were higher in this test than in subsequent ones probably due to anxiety In the second and third tests this difference diminished as resting heart rates on placebo approached those on perhexiline which remained unchanged

Heart rates at the highest work load achieved on placebo were compared with those at the same work load on perhexiline Eight of the ten showed lower rates with perhexiline and the difference in the whole group is significant for each test (Table III)

Heart rates at the point of angina were not significantly different and did not vary by more than ten beats per minute except in the two patients who *did not have lower* exercising heart rates on perhexiline (Patients 1 and 8 Table IV) Their heart rates at the point of angina were 11 and 30 beats per minute higher on perhexiline

Blood pressure readings used in the analysis were the mean of those recorded in the study room during the second and third tests No significant difference between resting or exercising systolic or diastolic blood pressures was found between the values recorded on perhexiline and those on placebo (Table V) The product of systolic blood pressure and heart rate at the highest comparable work load was signifi

Table II Resting heart rates (mean values for 10 patients)

Test	Placebo	Perhexiline	Differences between perhexiline and placebo
I	77 9	69 0	−8 9 $p < 0.01$
II	73 2	69 3	−3 9 p = N S
III	72 3	69 0	−3 3 p = N S

Table III Heart rates per minute at the highest comparable work load (mean values for 10 patients)

Test	Control	Placebo	Perhexiline	Difference p value
I	Load varying	104 0	96 8	−7 2 $p < 0.05$
II	Load varying	106 0	97 0	−9 0 $p < 0.001$
III	103 5	103 5	97 5	−6 2 $p < 0.05$

Table IV Heart rates per minute at the point of angina

Patient	Perhexiline	Placebo
1	139	128
2	111	105
3	106	110
4	109	103
5	111	112
6	81	8[illegible]
7	95	104
8	150	1[illegible]0
9	103	110
10	110	116
Mean	111	109

Table V Blood pressure results (mean values for 10 patients)

	Placebo	Perhexiline	Difference	Significance
Resting systolic (mm Hg)	136 8	136 3	−0 5	p = NS
Systolic at highest comparable load (mm Hg)	157 9	153 0	−4 9	p = NS
Resting diastolic (mm Hg)	83 8	85 9	+2 1	p = NS
Diastolic at highest comparable load (mm Hg)	97 7	93 7	−4 0	p = NS
Systolic at highest load (mm Hg) × heart rate	16 798	14 985	−1 813	p = < 0 01

cantly lower on perhexiline ($p < 0.01$) The forced expiratory volume in one second as a percentage of the forced vital capacity was greater than 75 per cent on placebo and perhexiline in all but one patient in whom it was 69 per cent on placebo and 75 per cent on perhexiline Pedometry revealed no evidence that the patients walked farther when taking perhexiline rather than placebo, even though all showed improvement in exercice tolerance

Discussion

Double blind studies may be imperilled by side effects or the success or the drug under study It is difficult to avoid this problem and in our trial it was possible to anticipate prior to analysis that the patient who withdrew was on the drug at the time, and in each of the others the correct order of administration for drug and placebo

The action of the drug was evident in all but the trial was designed to study its effects on heart rate and blood pressure and it was found that blood pressure was unaltered by perhexiline but that heart rates were changed

Resting rates were 9 per minute slower than on placebo in the first of the three tests, but this statistically significant difference all but disappeared in the next two tests as resting pulse rates on placebo fell It is possible that the patients were more relaxed in later tests on the same afternoon and that perhexiline abolished the resting tachycardia of mild anxiety or aware that they were probably on perhexiline they were more confident from the start

Perhexiline also slowed the exercising heart rate in all tests and at maximum comparable work load prior to developing angina an average over all rate reduction of 7 per minute was observed

At the point of angina however, heart rates were the same with perhexiline and placebo supporting the simple explanation that the drug delays angina by a reduction in the rate of rise in heart rate resulting from exercise and possibly emotion

There are no comparable reports on the effect of the drug on heart rate at the time of angina Three other studies on heart rate at rest and on exercise have however, been made Grupp and associates[9] gave 100 mg q d s of perhexiline to healthy volunteers tested on a treadmill they found no change in resting heart rates but a reduction in the tachycardia produced by exercise without any effect on blood pressure Winsor[5] gave the drug in the same dosage to angina patients also tested on a treadmill He similarly found no reduction in resting heart rate but a significant fall in exercise heart rate averaging 22 per minute more than that found by us Lyon and associates[3] found no consistent change in either resting or postexercise heart rate

Perhexiline has a direct effect on atrial muscle and is not thought to act through beta blockade[10] There are differences between the effects we found and those reported from the use of beta blocking drugs in patients with angina Using propranolol, Prichard and Gillam[11] found a dose related reduction in resting and exercising heart rates Similar reports with alprenolol came from Sealey and associates[12] and Sowton and Smithen[13] At effective dosage the reduction was of greater degree than foun by us with perhexiline but more import

all three report a reduction in heart rate at the point of angina in contrast to our findings

There are some points to be made against the premise that perhexiline acts solely by delaying the rise in exercise heart rate (1) This effect is modest (2) Perhexiline is sometimes effective in patients not helped by beta blockers known to cause greater reductions in heart rate (3) Perhexiline helped two of our patients without any effect on heart rates at rest or on exercise enabling greater exercise tolerance and heart rates 11 and 30 per minute faster than on placebo at the point of angina If this is not due to a natural remission we must look for another effect of perhexiline

Although powerful coronary vasodilator drugs such as dipyridamole have proved ineffective in angina glyceryl trinitrate has been shown to increase coronary flow in experimental myocardial infarction[14] It remains a possibility that the modest coronary vasodilator action of perhexiline may contribute to its action It has yet to be shown how perhexiline compares with the beta blocking drugs and whether their effects are additive

Summary

In patients with angina a double blind trial of the action of perhexiline maleate at rest and during exercise on a bicycle ergometer has shown a significant increase in exercise tolerance and a reduction in exercising heart rate but no reduction in heart rate at rest or at the point of angina and no change in blood pressure

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Table V. Blood pressure results (mean values for 10 patients)

	Placebo	*Perhexiline*	*Difference*	*Significance*
Resting systolic (mm. Hg)	136.8	136.3	−0.5	p = N.S.
Systolic at highest comparable load (mm. Hg)	157.9	153.0	−4.9	p = N.S.
Resting diastolic (mm. Hg)	83.8	85.9	+2.1	p = N.S.
Diastolic at highest comparable load (mm. Hg)	97.7	93.7	−4.0	p = N.S.
Systolic at highest load (mm. Hg) × heart rate	16,798	14,985	−1,813	p = < 0.01

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The forced expiratory volume in one second is a percentage of the forced vital capacity was greater than 75 per cent on placebo and perhexiline in all but one patient, in whom it was 69 per cent on placebo and 75 per cent on perhexiline. Pedometry revealed no evidence that the patients walked farther when taking perhexiline rather than placebo, even though all showed improvement in exercise tolerance.

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Perhexiline has a direct effect on atrial muscle and is not thought to act through beta blockade.[10] There are differences between the effects we found and those reported from the use of beta blocking drugs in patients with angina. Using propranolol Prichard and Gillam[11] found a dose related reduction in resting and exercising heart rates. Similar reports with alprenolol came from Sealey and associates[12] and Sowton and Smithen.[13] At effective dosage the reduction was of greater degree than found by us with perhexiline but, more important

all three report a reduction in heart rate at the point of angina in contrast to our findings

There are some points to be made against the premise that perhexiline acts solely by delaying the rise in exercise heart rate (1) This effect is modest (2) Perhexiline is sometimes effective in patients not helped by beta blockers known to cause greater reductions in heart rate (3) Perhexiline helped two of our patients without any effect on heart rates at rest or on exercise enabling greater exercise tolerance and heart rates 11 and 30 per minute faster than on placebo at the point of angina If this is not due to a natural remission we must look for another effect of perhexiline

Although powerful coronary vasodilator drugs such as dipyridamole have proved ineffective in angina glyceryl trinitrate has been shown to increase coronary flow in experimental myocardial infarction [14] It remains a possibility that the modest coronary vasodilator action of perhexiline may contribute to its action It has yet to be shown how perhexiline compares with the beta blocking drugs and whether their effects are additive

Summary

In patients with angina a double blind trial of the action of perhexiline maleate at rest and during exercise on a bicycle ergometer has shown a significant increase in exercise tolerance and a reduction in exercising heart rate but no reduction in heart rate at rest or at the point of angina and no change in blood pressure

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Tuberculoma of the heart

Report of 9 cases

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A tubercular granuloma (tuberculoma) in the myocardium is decidedly rare Autopsy studies carried out prior to introduction of specific antituberculous therapy, state that the myocardium is involved in less than 0 30 per cent of patients dying from tuberculosis [1,2] The introduction of specific chemotherapy has diminished the incidence even further [3] and over the last decade, these lesions have become the subject of single case reports [3-5] Myocardial tuberculomas have been directly responsible for death in a few instances The cause of death in these patients has been conduction disturbances [3] ventricular rupture [6] coronary artery occlusion [9] obstruction to pulmonary blood flow [8] and impaired myocardial contractility [9] Advances in surgical techniques have now made these lesions potentially correctable,[5] and heart block secondary to a critical lesion in the conduction system[3] may benefit from electrical pacing Optimal preoperative planning requires an awareness of the disease and precise delineation of the lesion by cardiac catheterization and angiographic techniques [5]

Since tuberculomas have seldom been diagnosed during life, the antemortem clinical features of nine patients with myocardial tuberculomas collected from the autopsy records of J J Hospital Bombay India are presented The literature pertaining to morbidity and mortality rate of tuberculomas located in various regions of the heart is reviewed

Material and methods

During a period of ten years (1961 to 1970) 9 333 autopsies were performed at the J J Group of Hospitals Bombay India and nine cases of myocardial tuberculomas were found The incidence of tuberculosis in the autopsy material was 7 9 per cent Table I summarizes some of the pathologic features observed in these 9 patients The lesions were located in all regions of the heart and varied in size from pea to lemon size The number of tuberculomas in a single heart varied from 1 to 7 The nodules were white to yellowish in color had a firm consistency presented an irregular surface and often had a caseous center Microscopically these nodules were generally composed of a central area of caseation At the periphery numerous

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Fig 1 Microphotograph of a tuberculoma showing caseous material in the center surrounded by Langhans giant cells epitheloid cells and lymphocites (Hematoxylin and eosin. Original magnification X480)

Table I Table of nine patients with myocardial tuberculomas

Serial no	*Patient initials*	*Age/sex*	*Site of myocardial tuberculoma*	*Endocarditis*	*Myocarditis*	*Pericarditis*	*Probable primary focus*
1	S P	8/F	Right atrium	+			Hilar glands lungs
2	S D	52/M	Right atrium			+	Hilar glands lungs
3	M A	3/M	Right ventricle				Hilar glands lungs
4	R. R	42/M	*Right ventricle*			+	*Hilar gland lungs*
5	P R	37/M	Right ventricle				Hilar glands lungs
6	C R	55/M	Left atrium		+		Hilar glands lungs
7	M M	5/M	Left ventricle				Miliary tuberculosis (?) blood borne
8	R C	0/ 1	Multiple			+	Hilar glands lungs
9	F D	45/M	Multiple			+	Hilar glands lungs

Acid fast bacilli identified

follicles consisting of epitheliod cells giant cells and lymphocytes were seen In some instances the outer *zone consisted of an* area of *epitheliod* and large round cells (Fig 1) In all patients an attempt was made to identify acid fast bacilli by application of Ziel Nielson stain however tubercule bacilli were identified in only 2 instances In the remaining patients the lesions were presumed to be tubercular because of the characteristic histologic picture along with an active focus of tuberculosis in the body A pericarditis of varying degree *in either the visceral or parietal* component of the pericardial sac was observed in four instances The endocardium remained intact in all but two patients A diffuse interstitial and parenchymal myocarditis was noted in one patient Histo*logically this myocardium* revealed an increase in fibrous tissue cellular infiltration and a moderate increase in giant cells

A resume of the pertinent clinical and pathologic features in the nine patients with myocardial tuberculomas follows A comment is made on the signs and symptoms that may be produced by tuberculomas located in various regions of the heart

Tuberculomas of the right atrium

Case 1 An 8-year old girl was admitted for investigation of *fever and puffiness of the face of a month s*

Tuberculoma of the heart

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Fig 3 Case 2 Large caseous tumor in the right atrium



Fig 4 A through C Cases 3 4 and 5 Tuberculomas in the right ventricular outflow tract (A and B) and anterior right ventricular myocardium (C)

tubercular complex and bilateral miliary tuberculosis

Case 4 A 42 year old man was admitted to the Tuberculosis Ward for therapy of pulmonary tuberculosis On cardiac auscultation a Grade 3/6 ejection systolic murmur was heard at the left sternal border The second heart sound was normally split with A_2 greater than P_2 The remainder of the cardiovascular examination was normal There was no cardiac failure The patient died a few days later from tuberculosis At autopsy a large tuberculoma measuring 4 cm. in length 2 cm in width and 1 cm in depth was seen in the anterior wall of the right ventricle A cut section revealed a cavity composed of necrotic material with a thick fibrotic wall (Fig 4B) Acid fast bacilli were recovered from this lesion

Case 5 The heart of a 37 year old man who died on arrival at the hospital showed a tuberculoma 2 cm by 2 cm by 1 cm in the anterior wall of the right ventricle (Fig 4C) The rest of the heart was normal An active tubercular lesion was present in the right upper lung

Comment In this series (5 patients two of whom had multiple tuberculomas) tuberculomas were most commonly seen in the right ventricle This observation is consistent with the findings of Weigert[13] and Ziegler[14] who considered the right ventricular myocardium to be the most common site especially in the region of the right conus arteriosus (Weigert tubercle) In two of our patients large tuberculomas



Fig 2 *Case 1* Open right atrium showing an ulcerating tuberculous mass with thrombus formation at the SVC RA junction

duration Physical examination revealed facial edema bilateral nonpulsatile neck vein engorgement and clubbing of the nailbeds The lymph glands in the left axilla were enlarged and matted Signs of a cavitating pulmonary lesion were detected in the right lung The cardiac examination was essentially normal except for the presence of a continuous murmur over the right second and third interspace A chest x ray confirmed the presence of a cavitating lesion in the right upper lung field The cardiac silhouette was normal A diagnosis of pulmonary tuberculosis with mediastinal compression was made following identification of acid fast bacilli in the sputum Anti tuberculous therapy was instituted unfortunately the patient expired after five days of a massive bout of hemoptysis

The heart at autopsy showed a spherical mass 1 cm in diameter in the right upper atrium that projected into the lumen of the superior vena cava A thrombus had developed over this mass and obstructed the flow of blood from the superior vena cava into the right atrium (Fig 2) The tuberculous nature of this lesion was established by the characteristic granulation tissue and presence of acid fast bacilli on microscopic examination

Case 2 The heart of a 52 year old man dying of bilateral pulmonary tuberculosis showed a large mass which filled the entire right atrial appendage (Fig 3) The cardiac lesion was not suspected prior to death and retrospectively the only clue to the lesion may have been the presence of long standing atrial fibrillation

Comment Anders[10] in his review of 72 patients with myocardial tuberculomas found the right atrium to be the most frequent site of involvement This was felt to be so because of the frequent involvement of the right mediastinal lymph nodes with spread to the right atrial myocardium Horn and Saphir[1] remarked about the rarity of endocardial ulceration In *Case 1* the endocardial continuity was disrupted with subsequent thrombus formation which extended into the SVC giving rise to a superior vena cava obstruction syndrome A similar case has not been previously reported In *Case 2* the tuberculoma occupied a significant cross section of the right atrial cavity such gross lesions may seriously interfere with atrial contraction as cited by Adamson[8] Both patients with right atrial tuberculomas had atrial fibrillation Gouley and associates[11] have commented that the occurrence of atrial ectopic beats in a patient with tuberculosis should alert one to the possibility of involvement of the myocardium The etiology of atrial arrhythmias may be secondary to irritability produced by the inflammatory process in the atrium or to destruction of the SA node[12] by tuberculous pathology Even though detailed histologic studies of the SA node were not carried out in *Case 1* the location of the tuberculoma at the SVC RA junction makes it interesting to speculate that the sinus node was perhaps infiltrated by tuberculous granulation tissue

Tuberculomas of the right ventricle

Case 3 A three year old boy was admitted in a debilitated state with a history of fever of fifteen days On examination the child was anemic and malnourished The lung fields were clear to percussion and auscultation Examination of the heart revealed a Grade 3/6 ejection systolic murmur over the pulmonic area and along the left sternal border The second heart sound was normally split with diminished intensity of the pulmonic component A diagnosis of pulmonic valve stenosis was made on the basis of the cardiac auscultatory findings and the etiology of fever was under investigation The child died 48 hours following admission At necropsy a lemon sized mass was noted in the right ventricular outflow tract (Fig 4 1) The lungs showed a primary

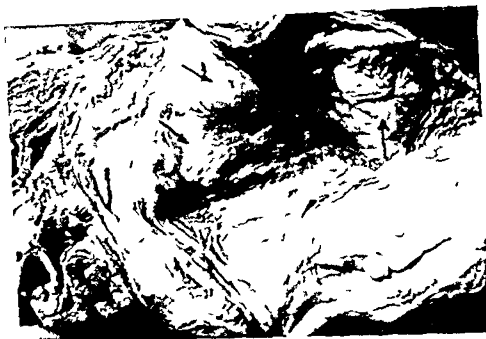


Fig 6 *Case 8* Open left ventricle showing multiple tuberculomas in the interventricular septum.



Fig 7 *Case 9* Two tuberculous nodules in the wall of the right ventr cle and left ventricular apex

appendage anterior right ventricular wall right ventricular infundibular area and apex of the left ventr cle The it t aventricular septum howed three tuberculomas (F g 6) the diameter of the large t one being 1½ cm There was an associated tubercular pericarditis and an active tubercular focus in the left upper lung

Case 9 The heart of a 45 year old man who died of chronic heart failure howed an area of localized pericarditis around the left ventricular apex A large tuberculoma (3 cm by 2 cm by 1 cm) was present in the anterior wall of the right ventricle and a second lesion (1 cm by 1 cm by 0 5 cm) at the apex of the left ventricle (Fig 7) The lungs showed chronic congestive changes and acti e tuberculosis of the right upper lung

Comment Extensive involvement of the intra ventricular septum was associated with complete A V block in a case reported by Kinare and Desh mukh[9] A detailed study of the conduction system in this case showed marked destruction of the A V node and His bundle by the tubercular process In *Case 8* besides the tubercular cardiac lesions there was no other demonstrable etiology for the patient s sudden and unexpected demise Even though de tailed studies of the conduction system were not carried out in this instance the sudden death in this patient may have been as a result of a lethal dis- turbance of cardiac conduction or rhythm

Multiple tuberculomas were seen in two of our pat ents Accord ng to Anders[10] it is not uncommon to see multiple tuberculomas in a single heart two to five being a fair average The greatest number recorded is 18 in a case of Fontoynot[11]

Summary

Nire patients with tuberculomas of the heart selected from autopsy material over a ten year period are presented The signs and symptoms produced by tuberculomas located in various regions of the heart are



Fig 5 *Case 6* Circumscribed tuberculous nodule in the wall of left atrium

were situated in the right ventricular outflow tract and had the auscultatory findings of right ventricular outflow tract obstruction Rawls and colleagues[5] reported a case similar to our patients in which a large myocardial abscess in a 36-year old woman with tuberculous lymphadenopathy partially obstructed the right ventricular outflow tract The clinically suspected hemodynamic alterations were confirmed by cardiac catheterization and right ventricular angiography The patient had an excellent response to isoniazid and Para aminosalicylic acid and to surgical drainage of the abscess

The presence of myocardial tuberculomas in patients with tuberculosis may also be suggested by the presence of right bundle branch block pattern or right heart strain on the electrocardiogram [6] Even though none of the lesions in this series had perforated tuberculomas have been known to perforate[6] into a cardiac chamber or into the pericardial cavity thus producing widespread dissemination acute tamponade or sudden death

Tuberculoma of the left atrium and myocarditis

Case 6 A 55 year old man was seen in the Emergency Room with acute pulmonary edema He looked severely anemic and had a thready pulse with a regular tachycardia of 150 beats per minute A chronic suppurating ulcer was noticed over the left mandibular area The patient died before complete examination could be carried out At necropsy both lung fields showed fibrocaseous tuberculosis most marked in the left lower lobe The heart was diffusely dilated and hypertrophied A peanut sized nodule was seen projecting from the wall of the left atrium into the cavity (Fig 5) The myocardium showed extensive scarring lymphocytic infiltration and giant cells Numerous tubercular granulomas were observed in the left atrial mass the mandibular ulcer and the lung

Comment Small tuberculomas in the left atrium may be detected at autopsy with no prior clinical evidence referrable to the heart.[11,16] However larger lesions in this location have seriously obstructed blood flow through the left atrium The cases of Maurocordatus[17] and Townsend[8] showed nodules of the left atrium so large that blood flow in the pulmonary veins was obstructed with resulting hemorrhage in the lungs and death from asphyxia

The etiology of acute pulmonary edema in *Case 6* was probably secondary to diffuse myocarditis Horn and Saphir[1] have cautioned against the diagnosis of tuberculous myocarditis in hearts with excessive connective tissue with a moderate amount of giant cells in the absence of caviation or acid fast bacilli Since similar changes will be accounted for by a previous diphtheria rheumatic fever scarlet fever coronary artery disease etc The myocarditis in our patient is therefore presumed to be tubercular in etiology because of the presence of acid fast bacilli in other areas of the body

Tuberculomas of the left ventricle

Case 7 Examination of the heart of a 5 year old boy who died of an automobile accident showed an elongated grayish yellow tumor like mass 3 5 cm by 1 3 cm by 1 2 cm extending from the left ventricular apex and deforming the posterior leaflet of the mitral valve The mass added 1 2 cm to the thickness of the left ventricular wall and was subendocardial throughout its cour e Microscopically the mass was composed of numerous granulomas with central caseation Miliary tubercles were widely distributed in the lungs and liver

Comment Although Raviart[18] regarded the left ventricle as the main site of myocardial tuberculous involvement it has seldom been found as the sole cardiac lesion by others [10,11] The reason for this is perhaps because the usual manner of spread of tuberculosis to the heart is from the right mediastinal lymph nodes [10] In *Case 7* the mediastinal lymph nodes were not involved and the patient had generalized miliary tuberculosis It is conceivable that in this particular instance the myocardial lesion was secondary to a blood borne infection However it should also be borne in mind that myocardial tuberculomas may be the means of disseminating this disease and setting up a generalized miliary inva ion as observed in one instance by Gouley and colleagues [11] The intact endocardium in our case suggests that the myocardial le ion was the result rather than the cause of generalized miliary tuberculosis

Multiple tuberculomas and tuberculomas of the intraventricular septum

Case 8 The heart of a 40-year old man who died suddenly and unexpectedly showed seven large tuberculomas The e were located in the right atrial

Total anomalous pulmonary venous drainage with ventricular septal defect

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The association of a large ventricular septal defect with total anomalous pulmonary venous drainage has been reported only rarely[1,2] The clinical implications of this combination of lesions have not been previously emphasized Three patients with total anomalous pulmonary venous drainage and ventricular septal defect have been documented at this institution within a one year period One infant had additional pulmonic stenosis All presented with clinical findings compatible with large left to right shunts The diagnosis was made at cardiac catheterization and angiocardiography in two patients but in the third infant the ventricular septal defect was not discovered until repeat catheterization following repair of the total anomalous pulmonary venous drainage

Incomplete diagnosis may result in serious errors in management The intent of this report is to outline an approach to diagnosis and treatment of these defects

Case reports

Case 1 L. A a one month-old Negro boy was admitted to Babies Hospital for cardiac evaluation A murmur had been noted on the first day of life and congestive heart failure and pneumonia occurred at nine days of age The infant was digitalized and treated with penicillin and kanamycin at another hospital Transfer to Babies Hospital was arranged when the baby did not improve

Physical examination disclosed a vigorous acyanotic infant in moderate respiratory distress The weight was 2 6 kilograms heart rate 120 respiratory rate 100 The lungs were clear to auscultation Examination of the heart revealed a grade III/VI blowing pansystolic murmur at the lower left sternal border S_2 was single The liver was palpable 3 cm below the right costal margin The chest x ray showed an enlarged heart with pulmonary vascular overcirculation An electrocardiogram (ECG) showed a QRS axis of +120 an RsR in V_1 and right ventricular predominance Oxygen saturation in room air was 90 per cent The infant showed no improvement on a maximal cardiotonic regimen Three days following admission cardiac catheterization and selective right ventricular angiocardiography demonstrated total anomalous pulmonary venous drainage via the coronary sinus Left ventricular angiocardiography was not performed The data are summarized in Table I

Three days following the cardiovascular study the total anomalous venous drainage was totally repaired by means of cardiopulmonary bypass The postoperative course was characterized by recurrent pneumonia and atelectasis with P_{CO_2}s ranging from 40 9 to 61 mm Hg Persistent pulmonary failure led to long term administration of high oxygen concentrations A lower left sternal border holosystolic murmur persisted Two months postoper

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specifically discussed with a view to early diagnosis and therapy The relevant literature is reviewed

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were heard over both posterior lung fields Cardiac examination revealed a prominent systolic thrill at the left lower sternal border The second sound was single A grade IV/VI rough holosystolic murmur was heard along the left lower sternal border The liver was palpable 7 cm below the right costal margin There was no cyanosis The peripheral pulses were strong and equal Chest x ray showed an enlarged heart with marked increase in prominence of the pulmonary vasculature (Fig 1) The ECG revealed the QRS to be +110° with right ventricular preponderance (Fig 2) P waves in Lead II were 2 5 mm and peaked

The infant improved following treatment with digoxin furosemide and oxygen One week following admission cardiac catheterization and right ventricular angiocardiography documented total anomalous pulmonary venous drainage to the right atrium (apparently via the coronary sinus) (Fig 3) The catheterization data showed right ventricular hypertension and some right ventricular outflow tract obstruction within a 52 mm peak systolic gradient between the pulmonary artery and the body of the right ventricle (Table I)

A selective left ventricular angiocardiogram was also performed which showed a large left to-right shunt at the ventricular level (Fig 4)

The infant s condition remained stable and he was discharged on digoxin three days following the procedure He is presently doing well at home at 18 months of age

Discussion

The reported incidence of total anomalous pulmonary venous drainage with a ventricular septal defect as the sole complicating lesion varies Brody[4] reviewing 102 cases of anomalous pulmonary venous drainage of which 37 were total found no case of associated ventricular septal defect Burroughs and Edwards[5] did not find a ventricular septal defect as a single associated malformation in their review of 188 cases of total anomalous pulmonary venous drainage although 66 had other multiple major cardiac anomalies including in many cases the asplenia syndrome In a review of 30 patients with total anomalous pulmonary venous drainage Gott and associates[6] found six cases to have associated anomalies but none was an isolated ventricular septal defect The extensive review of Nakib and colleagues[7] and Blake and colleagues[8] also failed to show ventricular septal defect alone as a frequent complicating lesion

On the other hand Bonham Carter and associates[1] in an analysis of 75 children with total anomalous pulmonary venous drainage found that of 17 with major associated anomalies four had ventricular



Fig 1 Admission chest roentgenogram (Case 3) showing cardiomegaly with increased vascularity

septal defect Our experience since 1966 consists of 19 patients with total anomalous pulmonary venous drainage three of whom had ventricular septal defects

When total anomalous pulmonary venous drainage with pulmonary hypertension exists as an isolated lesion we have reported in a previous publication that early surgical correction of the defect by means of cardiopulmonary bypass has been a successful method of treatment at this institution[9] However when a complicating ventricular septal defect is present this may not be the best approach to management Indeed failure to diagnose the additional anomaly may prove fatal if correction of the total anomalous venous drainage alone is undertaken

In all three of these cases the diagnosis of ventricular septal defect with left to right shunt was considered on the basis of the clinical presentation including especially the auscultatory findings In two of these cases however after the documentation of total anomalous pulmonary venous drainage during the initial catheterization the possibility of ventricular septal defect was not further investigated—partly in view of the supposed rarity of this association The murmurs were then attributed to tricuspid insufficiency In retrospect however the holosystolic left sternal border murmurs were not caused by tricuspid insufficiency but were secondary to the ventricular septal defects as initially suspected In one of these cases repeat catheterization did reveal the presence of the

Table I Cardiac catheterization data

Patient	SVC		RA		RV		PA		LA		LV		PVR (RU/M²)
	Sat*	P*	Sat	P	Sat	P	Sat	P	Sat	P	Sat	P	
L A													
No 1	81		85	†M = 6	89	65/12ED‡	88	65/24 $\overline{45}$	95	M = 3	96	[illegible]4/[illegible]ED	3 6
No 2	72	M = 2	73	M = 2	82	33/3ED	82	35/18 $\overline{28}$					2 2
N G	93			M = 5‖	93	102/7ED	87	85/45 $\overline{68}$	85	M = 7‖	83	110/10ED	4 4
R R	84§												
	69		97	M = 7	89	86/6¶ED	91	3[illegible]/10¶ $\overline{20}$		M = 7	98	86/-	0 9

*Sat = Oxygen saturation P = pressure
†M = mean
‡ED = End diastolic
§IVC
‖Not simultaneous
¶Direct withdrawal

atively a second catheterization was carried out and a left-to-right shunt at the ventricular level was suspected on the basis of oxygen saturation data The pulmonary artery pressure was only minimally increased (Table I) and pulmonary vascular resistance (PVR) was calculated at 2 2 resistance units (RU)

The infant continued to do poorly over the succeeding months Feedings were not taken well and respiratory distress continued Despite the use of a feeding gastrostomy the infant failed to thrive His physical status gradually deteriorated and he died 7½ months postoperatively

Postmortem examination The heart and lungs weighed 250 grams (normal = 119 ± 30) The total anomalous pulmonary venous drainage was well repaired and there was no visible obstruction to pulmonary venous return A ventricular septal defect 0 8 cm in diameter was found above the crista supraventricularis The right ventricle was dilated as was the main pulmonary artery which was larger in diameter than the ascending aorta The left ventricle was slightly larger than the right

Microscopic examination of the lungs revealed hypertrophy of arteries and veins with mild muscular arterial hyperplasia (Stage II Pulmonary Vascular Disease)[3] as well as septal and focal interlobular fibrosis These fibrotic changes may represent the effects of prolonged oxygen administration

Case 2 N G a 4 month old Caucasian girl was admitted to Babies Hospital for cardiac surgery The history was unremarkable until 2½ months of age when tachypnea and increasing fatiguability were noted A murmur compatible with the clinical diagnosis of ventricular septal defect was heard one month later

The infant was admitted to another hospital and digitalized with minimal improvement Cardiac catheterization and angiocardiography showed total anomalous pulmonary venous drainage via a left superior vena cava A left ventricular angiocardiogram was not done She was then transferred to Babies Hospital

On admission the infant was noted to be acyanotic and in mild respiratory distress The weight was 4 1 kilograms heart rate 150 respiratory rate 70 The lungs were clear to auscultation Examination of the heart revealed a visible right ventricular impulse a grade III/VI holosystolic murmur at the left sternal border and a single second sound There was no hepatosplenomegaly or peripheral edema

The ECG showed an axis of +135 with right ventricular enlargement The T waves were upright in V_1 A chest x-ray showed cardiomegaly with a wide superior mediastinum and pulmonary vascular engorgement

Because of the murmur suggestive of ventricular septal defect the infant was recatheterized The catheterization data confirmed total anomalous pulmonary venous drainage via the superior vena cava with pulmonary hypertension (Table I) An angiocardiogram performed with the catheter in the left ventricle demonstrated the presence of a large high ventricular septal defect with left to right shunt Two days later an open heart operation was performed in an attempt at total correction In addition to the total anomalous pulmonary venous drainage to the left innominate vein a large membranous ventricular septal defect was found Correction of these anomalies required 80 minutes of cardiopulmonary bypass Four hours postoperatively the patient became severely acidotic Multiple cardiac arrests ensued and she died eight hours postoperatively An autopsy was not obtained

Case 3 R R a 2 month old Caucasian boy was admitted to Babies Hospital because of congestive heart failure He was the product of an uncomplicated term pregnancy and appeared normal at birth A heart murmur was noted at one week of age but the infant thrived at home with good weight gain One week prior to admission tachypnea fatigue with feedings and excessive sweating were noted

Physical examination revealed a well developed well nourished acyanotic infant in moderate respiratory distress The weight was 4 6 kilograms heart rate 170 respiratory rate 90 Bilateral moist rales



Fig 4 Frontal (left) and lateral (right) angiocardiograms (Case 3) during injection of radiopaque contrast material into the relatively small left ventricle A substantial left to-right shunt via a ventricular septal defect opacifies the right ventricle and pulmonary arterie The right ventricular outflow tract gradient was identified by catheter withdrawal

lar stroke output tends to increase blood flow in the pulmonary circuit and at the same time reduce the systemic output Such hemodynamics require relatively large flows from right to left across the inter atrial septum If resistance in the pulmo nary *circuit is high left to right shunting* via the ventricular septal defect would be limited and in rare instances it might be speculated that right to left shunting through such a ventricular septal defect would occur reducing pulmonary blood flow while augmenting systemic output

In the absence of a ventricular septal defect surgical elimination of the large pulmonary vein-right atrial shunt reduces right ventricular return and right ventric ular output The pulmonary artery pressure is correspondingly reduced even assuming no change in pulmonary vascular resistance When a large ventricular septal defect is present however the reduced right ven tricular output would tend to be matched by a corresponding increase in the left to right shunt via the ventricular septal defect Thus by repair of the anomalous venous connections alone, the work of pumping a large left to right shunt is *shifted from the right to the left ventricle* This radical change in the output require ments for the left ventricle may not be tolerated In Case 1 the limited size of the ventricular septal defect probably pre vented immediate catastrophe following repair of the total anomalous pulmonary venous drainage and death seemed unre lated to the interventricular communica tion

Since the ventricular septum is usually intact in total anomalous pulmonary ve nous drainage palliative pulmonary artery banding has not been considered However when a large ventricular septal defect com plicates total anomalous pulmonary venous drainage in a critically ill infant with pul monary hypertension and congestive heart failure, a palliative operation—banding of the pulmonary artery—might be consid ered This procedure would be expected to reduce both pulmonary blood flow and pulmonary hypertension while simulta neously augmenting systemic output Such beneficial effects are suggested by the favorable course of R R (Case 3) who had a moderate obstruction and pressure gra dient across the pulmonary outflow tract

Summary

Three patients with total anomalous pul monary venous drainage and ventricular septal defect with left to right shunt are presented The ventricular septal defect was diagnosed with left ventricular angio cardiography in two patients and confirmed on postmortem examination in the third

The complex hemodynamic implications of this combination of lesions are discussed Pulmonary artery banding is suggested as a possible method of management in early infancy

When total anomalous pulmonary venous drainage is demonstrated in infants initially suspected of having large ventricular septal defects on the basis of *auscultation* left ventricular angiocardiography is manda tory Preoperative diagnosis of a compli



Fig 2 Admission ECG (Case 3) Axis +110° Right ventricular preponderance P waves are peaked in Lead II



Fig 3 Frontal angiocardiogram (Case 3) showing late phase of pulmonary vein opacification 3 sec following injection of radiopaque contrast material into right ventricle The expected opacification of the left atrium is not seen Instead the pulmonary veins opacify the right atrium (*RA*) apparently via the coronary sinus (*arrows*)

complicating ventricular septal defect prior to the attempt at corrective surgery

In the third case, the initial diagnosis of ventricular septal defect was confirmed by a left ventricular angiocardiogram in the early phases of the catheterization, and total anomalous pulmonary venous drainage was not really suspected until subsequent completion of the right sided study

Since left and right ventricular oxygen saturations are similar in total anomalous pulmonary venous drainage oxygen saturation determinations cannot be expected to be of great value in the detection of a complicating ventricular septal defect Oxygen saturation data however might have been of value in one of our patients (N G Case 2), in whom a consistent "step down" in saturation was noted on entering the pulmonary artery from the right ventricle (Table I) In this instance left heart saturations were somewhat lower than those in the right ventricle—presumably due to streaming of less saturated inferior vena caval blood into the left heart via the foramen ovale Thus a left to right shunt at the ventricular level may have been paradoxically responsible for the modest fall or "step down" of oxygen saturation in the pulmonary artery

The hemodynamic significance of a large ventricular septal defect in total anomalous pulmonary venous drainage is complex In our cases left to right shunts occurred via the ventricular septal defect This diversion of some of the left ventricu

Experimental and laboratory reports

Early arrhythmias following experimental coronary occlusion in conscious dogs and their modification by beta-adrenoceptor blocking drugs*

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The influence of the beta adrenoceptor blocking agents in experimental coronary occlusion has been studied by many investigators[1-8] but all of their experiments were performed either in anesthetized open chest animals or in conscious animals one to five days after coronary occlusion As early as 1939 it was pointed out that general anesthesia by itself significantly reduces the incidence of ventricular arrhythmias following the ligation of either branch of the left coronary artery[9] It has also been shown that the hemodynamic effects of the beta adrenoceptor blocking drugs differ considerably between conscious and anesthetized animals[10] Harris and associates[11] described three phases following abrupt coronary occlusion in anesthetized dogs first the period of marked danger from ventricular ectopic beats and fibrillation usually lasting for 10 to 15 minutes from the time of occlusion the second period with a decline of ectopic activity and lasting until the development of ventricular tachycardia—between 4 5 and 8 hours and a third phase characterized by delayed arrhythmias lasting for two to five days Those studies done on the second or third day of coronary occlusion thus missed the phase where the danger of ventricular ectopic beats fibrillation and sudden death is greatest

The present investigation was designed to evaluate the influence of a group of beta adrenoceptor blocking drugs on the arrhythmias that complicate the early phase of acute coronary occlusion in *conscious* dogs The particular drugs selected for study permitted a definition of the relative roles played by generalized beta adrenoceptor blockade by cardioselective beta blockade and by the local anesthetic properties of these substances Their effect on heart rate blood pressure

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*These tudie r se ted part t th meeting of the Roy l C ll g of Phy cia s d Surg ons of Canada J ry 29 D d t the Ca d F d t of B logical Soc t s, i J ne 1970 both t Montr al nd at the I t rn nal Symposi m Ather scle osis, i J ne 1971 at T ont C nada.
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cating ventricular septal defect is essential to optimal management

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Experimental and laboratory reports

Early arrhythmias following experimental coronary occlusion in conscious dogs and their modification by beta-adrenoceptor blocking drugs*

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The influence of the beta adrenoceptor blocking agents in experimental coronary occlusion has been studied by many investigators[1-8] but all of their experiments were performed either in anesthetized open chest animals or in conscious animals one to five days after coronary occlusion As early as 1939 it was pointed out that general anesthesia by itself significantly reduces the incidence of ventricular arrhythmias following the ligation of either branch of the left coronary artery[9] It has also been shown that the hemodynamic effects of the beta adrenoceptor blocking drugs differ considerably between conscious and anesthetized animals[10] Harris and associates[11] described three phases following abrupt coronary occlusion in anesthetized dogs first the period of marked danger from ventricular ectopic beats and fibrillation usually lasting for 10 to 15 minutes from the time of occlusion the second period with a decline of ectopic activity and lasting until the development of ventricular tachycardia—between 4 5 and 8 hours and a third phase characterized by delayed arrhythmias lasting for two to five days Those studies done on the second or third day of coronary occlusion thus missed the phase where the danger of ventricular ectopic beats fibrillation and sudden death is greatest

The present investigation was designed to evaluate the influence of a group of beta adrenoceptor blocking drugs on the arrhythmias that complicate the early phase of acute coronary occlusion in *conscious* dogs The particular drugs selected for study permitted a definition of the relative roles played by generalized beta adrenoceptor blockade by cardioselective beta blockade and by the local anesthetic properties of these substances Their effect on heart rate, blood pressure

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**Ontario Heart Foundation Fellow

Table I The effect of various drugs compared to normal saline injection on the mean heart rate of conscious dogs

Drug or saline	Before	After	Mean change	p value of the difference
	Mean heart rate ± standard error of the mean			
1 Normal saline	121 9 ± 5 0	123 2 ± 5 0	+ 1 3 ± 2 2	> 0 5
2 *dl* propranolol 0 1 mg /kg	107 4 ± 4 8	99 6 ± 4 6	− 7 8 ± 2 8	< 0 01
3 *dl* propranolol 1 0 mg /kg	122 5 ± 7 3	110 9 ± 5 6	−11 6 ± 3 8	< 0 02
4 MJ 1999 0 2 mg /kg	118 7 ± 2 7	112 8 ± 2 8	− 6 0 ± 2 0	< 0 01
5 MJ 1999 3 2 mg /kg	95 4 ± 6 5	89 6 ± 4 4	− 5 8 ± 5 3	> 0 3
6 *d* propranolol 0 07 mg /kg	117 3 ± 9 5	112 3 ± 9 5	− 5 1 ± 5 1	> 0 3
7 MJ 1999 0 2 mg /kg + *d* propranolol 0 07 mg /kg	114 4 ± 5 0	111 0 ± 4 3	− 3 4 ± 3 1	> 0 2
8 AY 21 011 1 4 mg /kg	109 6 ± 7 1	105 8 ± 7 2	− 3 8 ± 2 6	> 0 1

and electrocardiogram were measured The mortality rates found with these agents in experimental coronary occlusion in conscious dogs are published elsewhere [12]

Methods and materials

Adult mongrel dogs (5 to 18 kilograms) were anesthetized with pentobarbital (25 to 30 mg per kilogram of body weight) and a loose ligature was placed around the circumflex branch of the left coronary artery at its origin under direct vision as described previously [9, 12] The ends of the ligature were exteriorized the chest was closed in layers, and the animal was allowed to recover for 48 to 72 hours Then the right femoral artery and vein were cannulated under local anesthesia All drugs were administered through the venous catheter Direct arterial pressure (Statham P23 db transducer) and electrocardiogram (usually Lead II from subcutaneous needle electrodes) were recorded simultaneously on a Sanborn (Model 67 1600) multichannel direct writer Magnetic tape recordings (Sony) made at the same time were used for subsequent detailed analysis of arrhythmias

Control animals received normal saline and treated animals received an appropriate amount of the assigned drug dissolved in normal saline in exactly the same manner All doses are expressed in terms of the salt used Five minutes later the exterior ends of the ligature were pulled to totally occlude the artery Blood pressure and ECG were recorded continuously for the first 10 minutes after coronary occlusions and every 15 minutes thereafter for a period of two hours or until death Continuous tape recordings of ECG were made throughout the two hour period of observation in the first 65 experiments, but subsequently, this was reduced to one hour

A total of 141 dogs was randomly allocated as follows

- Group 1 normal saline 2 to 3 ml (n = 25)
- Group 2 *dl* propranolol (Inderal) * 0 1 mg per kilogram of body weight (n = 25)
- Group 3 *dl* propranolol * 1 0 mg per kilogram of body weight (n = 10)
- Group 4 MJ 1999 (Sotalol) † 0 2 mg per kilogram of body weight (n = 25)
- Group 5 MJ 1999 † 3 2 mg per kilogram of body weight (n = 12)
- Group 6 *d* propranolol * 0 07 mg per kilogram of body weight (*n* = 16)
- Group 7 *d* propranolol 0 07 mg per kilogram of body weight + MJ 1999 0 2 mg per kilogram of body weight (n = 12)
- Group 8 AY 21 011 (Practolol) * 1 4 mg per kilogram of body weight (n = 16)

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†Mead Johnson & Co Evansville Ind

The doses of the drugs were selected from the results of preliminary experiments in conscious dogs in which their ability to antagonize the chronotropic effect of isoproterenol (1.5 µg per kilogram of body weight) was determined. The doses used in Groups 2, 4, and 8 were equiactive and caused 50 per cent blockade of isoproterenol induced tachycardia and those used in Groups 3 and 5 caused nearly 100 per cent blockade. The dose of *d* propranolol used in Groups 6 and 7 has been shown to have an equal local anesthetic effect to that of the *dl* propranolol used in Group 2.[18]

For detailed analysis of arrhythmias the magnetic tape was played back using a Philips tape recorder with attached arrangement for visual display of electrocardiogram on a Dumont 401B oscilloscope. A Hewlett Packard electrocardiogram machine in the system allowed direct write-out of any segment of taped electrocardiogram and a Philips Analog 7 recorder was used for rerecording and playbacks at slower than recorded rate when required.

The significance of the effects on heart rate, blood pressure, and PR interval was tested by Student's t test using paired data and the mean changes were subjected to over all analysis of variance. The immediate effects of coronary occlusion on the heart rate and blood pressure were analyzed in the same way. The Chi square method was used to test the significance of the difference in the number of experimental animals exhibiting a particular cardiac arrhythmia. For numerical analysis the ventricular ectopic beats were expressed in terms of their frequency per minute in each dog during the three 5 minute periods following coronary occlusion. The difference between each of the parameters tested was considered significant only when p values were less than 0.05.

Results

The effects of beta-adrenoceptor blocking drugs in conscious dogs. No unusual general effects—e.g., vomiting, diarrhea, excitement, tremor, convulsions, stupor, or shortness of breath were noted following the administration of the drugs used in this study.

There was a decrease in the mean heart rate (Table I) and an increase in both systolic and diastolic blood pressures (Table II) following the administration of the beta adrenoceptor blocking drugs. When the changes induced by normal saline were compared with the changes caused by all the treatments, taken as a group, the difference was significant ($p < 0.05$). Except for AY 21,011 all beta adrenoceptor blocking drugs in the doses used caused a significant prolongation of the PR interval (Table III).

The effects of sudden coronary occlusion in conscious dogs. There was a significant increase in heart rate in all groups immediately following the coronary occlusion, reaching a peak between 30 and 120 seconds, then gradually returning towards the pre-occlusion level (Fig. 1).

There was a decrease in both systolic and diastolic blood pressures in all groups immediately following the coronary occlusion, reaching its lowest level within two minutes and gradually coming back towards but not reaching the pre-occlusion level within the 2 hour period (Fig. 2*A* and *B*).

Systolic pressures decreased more than diastolic so that the pulse pressure following coronary occlusion remained below the pre-occlusion level during the period of observation. For the systolic blood pressure, the difference between the pre-occlusion level and the maximal drop following coronary occlusion, analyzed as paired data, was significant in all groups ($p < 0.02$ to 0.001) except in the group treated with *d* propranolol ($p > 0.05$), but there were no significant differences among the various treatment groups. The maximal fall in diastolic blood pressure following coronary occlusion was statistically significant in Groups 1, 2, and 7 but again was not significantly different among these groups.

Cardiac arrhythmias. The incidence of ventricular fibrillation (VF) in Groups 2, 4, 5, 7, and 8 was significantly lower than that in Groups 1 and 6 (Table IV). The 40 per cent incidence of VF in Group 3 when contrasted with the 72 per cent in the control group approached significance.

Ventricular ectopic beats were classified into (1) ventricular premature beats (PVB) when they appeared singly or in groups of three or less and (2) ventricular tachycardia (VT) when they occurred in groups of four or more. When present they usually appeared within seconds of coro

Table IIA The effect of various drugs compared to normal saline on the blood pressure in conscious dogs

Drug or saline	Before	After	Mean change	p value of the difference
Mean systolic blood pressure (mm Hg) ± standard error of the mean				
1 Normal saline	153 4 ± 4 8	154 3 ± 4 3	+0 9 ± 2 0	> 0 5
2 *dl* propranolol 0 1 mg/Kg	154 9 ± 4 0	164 8 ± 4 2	+9 9 ± 1 7	< 0 001
3 *dl* propranolol 1 0 mg/Kg	155 0 ± 6 7	161 4 ± 5 6	+6 4 ± 2 4	< 0 05
4 MJ 1999 0 2 mg/Kg	147 1 ± 3 7	151 8 ± 3 9	+4 6 ± 1 9	< 0 05
5 MJ 1999 3 2 mg/Kg	158 5 ± 6 0	161 0 ± 7 4	+2 5 ± 4 7	> 0 5
6 *d* propranolol 0 7 mg/Kg	164 0 ± 6 7	168 5 ± 8 1	+4 5 ± 3 3	> 0 1
7 MJ 1999 0 2 mg/Kg + *d* propranolol 0 07 mg/Kg	164 3 ± 5 5	170 0 ± 6 8	+5 7 ± 4 4	> 0 2
8 Ay 21 011 1 4 mg/Kg	162 1 ± 5 6	168 6 ± 5 8	+6 5 ± 3 4	> 0 1

Table IIB The effect of various drugs compared to normal saline on the blood pressure in conscious dogs

Drug or saline	Before	After	Mean change	p value of the difference
Mean diastolic blood pressure (mm Hg) ± standard error of the mean				
1 Normal saline	91 0 ± 3 2	92 0 ± 3 2	+ 1 0 ± 2 0	> 0 5
2 *dl* propranolol 0 1 mg/Kg	92 6 ± 2 9	102 7 ± 3 3	+10 1 ± 1 8	< 0 001
3 *dl* propranolol 1 0 mg/Kg	91 0 ± 3 1	97 4 ± 3 8	+ 6 4 ± 1 5	< 0 01
4 MJ 1999 0 2 mg/Kg	83 4 ± 2 6	89 4 ± 2 8	+ 6 0 ± 1 6	< 0 001
5 MJ 1999 3 2 mg/Kg	86 3 ± 3 0	92 7 ± 5 0	+ 6 3 ± 4 5	> 0 1
6 *d* propranolol 0 07 mg/Kg	95 5 ± 4 5	95 8 ± 3 9	+ 0 3 ± 2 2	> 0 5
7 MJ 1999 0 2 mg/Kg + *d* propranolol 0 07 mg/Kg	95 8 ± 4 2	106 2 ± 5 7	+10 3 ± 6 6	> 0 1
8 Ay 21 011 1 4 mg/Kg	89 5 ± 3 4	97 1 ± 3 3	+ 7 6 ± 3 3	< 0 05

Table III The effect of various drugs compared to normal saline on the mean PR interval in conscious dogs

Drug or saline	Before	After	Mean change	p value of the difference
Mean PR interval (msec) ± standard error of the mean				
1 Normal saline	94 7 ± 2 5	97 8 ± 3 0	+ 2 9 ± 1 7	> 0 05
2 *dl* propranolol 0 1 mg/Kg	110 0 ± 4 4	121 3 ± 4 4	+11 3 ± 1 4	< 0 001
3 *dl* propranolol 1 0 mg/Kg	102 5 ± 3 0	113 9 ± 3 6	+11 4 ± 1 7	< 0 001
4 MJ 1999 0 2 mg/Kg	95 4 ± 2 8	105 1 ± 3 4	+10 0 ± 1 4	< 0 001
5 MJ 1999, 3 2 mg/Kg	110 6 ± 7 1	121 5 ± 6 1	+10 9 ± 2 7	< 0 01
6 *d* propranolol, 0 07 mg/Kg	102 4 ± 5 5	105 7 ± 5 9	+ 3 3 ± 1 6	< 0 05
7 MJ 1999, 0 2 mg/Kg + *d* propranolol 0 07 mg/Kg	95 7 ± 3 8	106 5 ± 4 6	+10 7 ± 1 8	< 0 001
8 Ay 21 011 1 4 mg/Kg	102 4 ± 6 1	103 9 ± 5 4	+ 1 5 ± 1 7	> 0 3

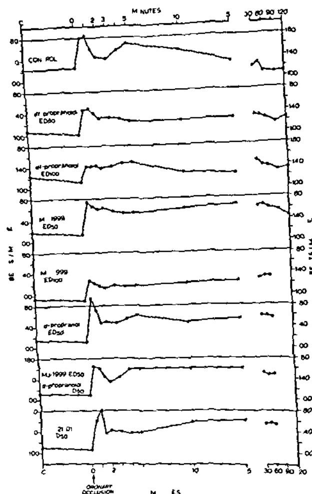


Fig 1 Time-course of the mean heart rate in various groups C = ba e line value O = coronary occlu ion C to O = effect of normal saline or drug Minutes indicate time from coronary occlusion

Table IV The incidence of ventricular fibrillation following sudden occlusion of the circumflex branch of the left coronary artery in conscious dogs

Group	Number of dogs	Ventricular fibr llation		Signifi ance of the difference contr l vs treatment
		Number	Per cent	
1 Control	25	18	72	
2 *dl* propranolol 0 1 mg /kg	25	5	20	p < 0 001
3 *dl* propranolol 1 0 mg /kg	10	4	40	0 05 < p < 0 1
4 MJ 1999 0 2 mg /kg	25	7	28	p < 0 005
5 MJ 1999 3 2 mg /kg	12	2	17	p < 0 005
6 *d* propranolol	16	11	69	p > 0 75
7 MJ 1999 0 2 mg /kg + *d* propranolol 0 07 mg /kg	12	2	17	p < 0 005
8 AY 21 011 1 4 mg /kg	16	3	19	p < 0 001

The d ff nce i the inc d e of ent ic l fib ill tio bet een the variou g oup l ghly ificant (p < 0 001 by o rall Chi sq t st)

Table IIA The effect of various drugs compared to normal saline on the blood pressure in conscious dogs

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Table III The effect of various drugs compared to normal saline on the mean PR interval in conscious dogs

Mean PR interval (msec) ± standard error of the mean				
Drug or saline	*Before*	*After*	*Mean change*	*p value of the difference*
1 Normal saline	94 7 ± 2 5	97 8 ± 3 0	+ 2 9 ± 1 7	> 0 05
2 *dl* propranolol 0 1 mg /Kg	110 0 ± 4 4	121 3 ± 4 4	+11 3 ± 1 4	< 0 001
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8 Ay 21 011 1 4 mg /Kg	102 4 ± 6 1	103 9 ± 5 4	+ 1 5 ± 1 7	> 0 3

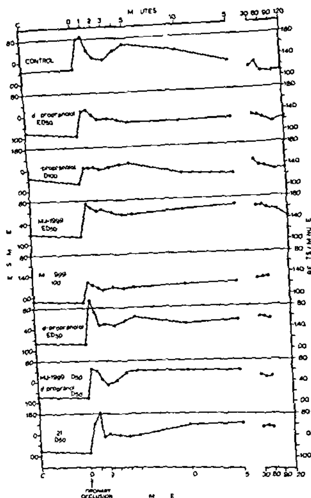


Fig 1 Time course of the mean heart rate in various groups C = base line value O = coronary occlusion C to O = effect of normal saline or drug Minutes indicate time from coronary occlusion

Table IV The incidence of ventricular fibrillation following sudden occlusion of the circumflex branch of the left coronary artery in conscious dogs

Group	Number of dogs	Ventricular fibrillation		Significance of the difference control vs treatment
		Number	Per cent	
1 Control	25	18	72	
2 *dl* propranolol 0 1 mg/Kg	25	5	20	$p < 0.001$
3 *dl* propranolol 1 0 mg/Kg	10	4	40	$0.05 < p < 0.1$
4 MJ 1999 0 2 mg/Kg	25	7	28	$p < 0.005$
5 MJ 1999 3 2 mg/Kg	12	2	17	$p < 0.005$
6 *d* propranolol	16	11	69	$p > 0.75$
7 MJ 1999 0 2 mg/Kg + *d* propranolol 0 07 mg/Kg	12	2	17	$p < 0.005$
8 \\ 21 011 1 4 mg/Kg	16	3	19	$p < 0.001$

The diff[illegible] the incidence of ventricular fibrillation between the [illegible] (p < 0 001 by overall Chi square test)

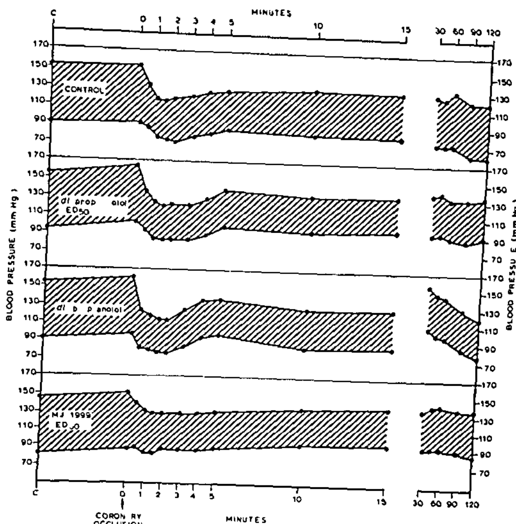


Fig. 2A. Time course of the mean systolic and diastolic blood pressure in various groups. Abbreviations are the same as in Fig. 1.

nary occlusion rapidly increased in frequency reaching peaks at 2 to 5 minutes and then gradually decreased in frequency, there being very few ectopic beats beyond 15 minute period following coronary occlusion (Fig. 3A and B). Ventricular ectopic beats were encountered in 69 to 92 per cent of dogs in the various groups (Table V). Ventricular tachycardia was noted in 12 to 72 per cent of animals in the various groups, being lowest in Groups 2 and 5.

The total number of ectopic beats per dog per minute, without regard to type (all ectopic beats) during the first, second and third 5 minute periods is shown in Table VI. When the incidence of all ectopic beats within the first five minutes in the control group is compared with all other groups taken together, the difference is significant ($p < 0.05$) because of the low incidence in Groups 2, 5 and 6.

The number of PVB per minute during the first, second and third 5 minute periods is shown in Table VII. The difference in their incidence between groups is not statistically significant in any of the three 5 minute periods.

When the incidence of ventricular tachycardia in the control group during the first 5 minute period is compared with that in all other groups taken together, the difference is significant ($p < 0.01$) (Table VIII). The incidence of this arrhythmia in the second and third 5 minute periods was very low.

No dog in Groups 1, 4, 6, and 7 had atrioventricular block. Five out of ten dogs treated with the higher dose of *dl* propranolol developed progressive first, second and third degree atrioventricular block, three ending in cardiac standstill. Four out of sixteen dogs treated with AY 21 011 developed progressive heart block, two ending in cardiac standstill. Of the two

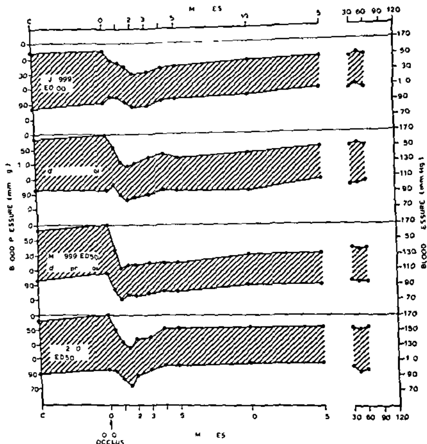


Fig 7B Time course of the mean systolic and diastolic blood pressure in various groups Abbreviations are the same as in Fig 1

dogs in the group treated with 0 1 mg per kilogram of body weight *dl* propranolol developing heart block one ended in cardiac standstill The incidence of severe heart block in Groups 3 and 8 is significantly higher than that in the control group ($p < 0.005$)

No dog in the control group showed sinus arrest but episodes of sinus arrest were noted in the remaining groups one dog in Group 4 two in each of the Groups 2 3 5 and 6 three in Group 8 and four in Group 7

Atrial tachycardia was noted in one dog in each of Groups 1 2 and 6 and atrial fibrillation in one dog in Group 2

Discussion

The effects of the drugs on the cardiovascular system are comparable to those in other studies [2 14] but the extent of reduction in heart rate was not always as great The reduction in heart rate was statistically significant only with the lower dose of MJ 1999 and the two doses of *dl* propranolol Despite the fact that AY 21 011 possesses a mild intrinsic sympathomimetic effect and has been shown to increase the heart rate in anesthetized cats [5] in most clinical studies it reduced the heart rate [15 17]

The rise of blood pressure after these drugs may be explained by an exaggerated alpha receptor response of the peripheral blood vessels to catecholamines [18] The fact that the larger doses of *dl* propranolol and MJ 1999 caused less elevation than the lower doses is most likely due to a greater fall in cardiac output The only discernible change in the electrocardiogram was a significant prolongation of the PR *interval* in all groups except the AY 21 011 (probably because of its intrinsic sympathomimetic action) [19] These results are similar to those reported by others [20 21]

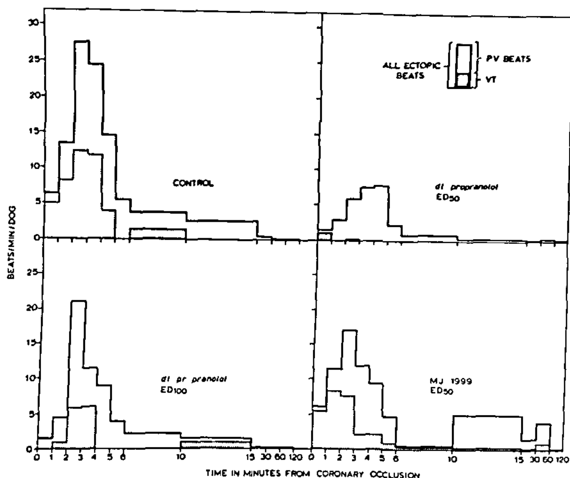


Fig 3A Ventricular ectopic beats following sudden coronary occlusion expressed in terms of beat /min /dog *Top time* = all ectopic beats *hatched area* = ectopic beats appearing in groups of four or more—ventricular tachycardia (*VT*) *clear area* = ectopic beats appearing singly or in groups of three or less—premature ventricular beats *(PVB)*

Table V Incidence of ventricular ectopic beats

Group	Number of dogs	Premature ventricular beats		Ventricular tachycardia	
		Number	Per cent	Number	Per cent
1 Normal saline	25	21	84	16	64
2 *dl* propranolol 0 1 mg /Kg	25	17	68	3	12
3 *dl* propranolol 1 0 mg /Kg	10	8	80	4	40
4 MJ 1999 0 2 mg /Kg	25	23	92	18	72
5 MJ 1999 3 2 mg /Kg	12	9	75	3	2
6 *d* propranolol 0 07 mg /Kg	16	11	68 8	6	37 5
7 MJ 1999 0 2 mg /Kg + *d* propranolol 0 07 mg /Kg	12	10	83 3	6	50
8 AY 21 011 1 4 mg /Kg	16	12	75	9	56 3

The temporal distribution of ventricular ectopic beats following sudden coronary ligation in the present study agrees with that described in anesthetized dogs[11] Multiple factors are probably involved in the production of ectopic impulses after coronary occlusion Certainly the catecholamines and the cardiac sympathetic nerves seem to be very important in the genesis of ectopic beats and ventricular fibrillation during the early phases[7, 2, 26] Although the doses of beta blocking agents

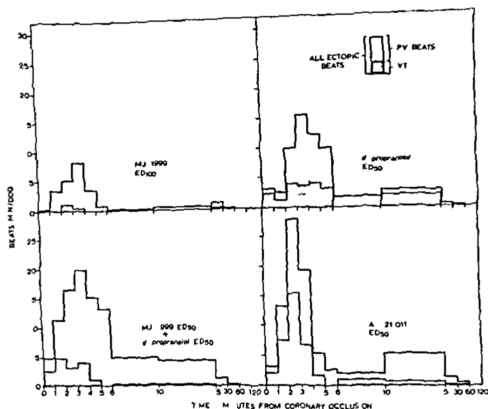


Fig 3B See legend for Fig 3A

Table VI All ventricular ectopic beats (± standard error of the mean) per dog per minute following occlusion

Group	First 5 minutes		Second 5 minutes		Third 5 minutes	
	(number/min)	p	(number/min)	p	(number/min)	p
1 Normal saline	16 06 ±3 3		4 18 ±2 13		2 26 ±2 09	
2 *dl* propranolol 0 1 mg/kg	5 12 ±1 38	<0 005	1 03 ±0 41	>0 1	0 2 ±0 1	>0 3
3 *dl* propranolol 1 0 mg/kg	11 32 ±5 00	>0 4	2 46 ±1 5	>0 3	1 49 ±1 01	>0 7
4 MJ 1999 0 2 mg/kg	13 23 ±4 0	>0 5	2 31 ±1 27	>0 5	4 84 ±1 86	>0 3
5 MJ 1999 3 2 mg/kg	4 72 ±1 59	<0 005	0 16 ±0 09	>0 05	0 42 ±0 32	>0 3
6 *d* propranolol 0 07 mg/kg	6 51 ±2 92	<0 05	7 99 ±6 03	>0 5	22 53 ±21 89	>0 3
7 MJ 1999 0 2 mg/kg + *d* propranolol 0 07 mg/kg	13 02 ±4 6	>0 5	6 33 ±3 8	>0 5	4 24 ±2 37	>0 3
8 AY 21 011 1 4 mg/kg	12 89 ±3 63	>0 5	1 4 ±0 82	>0 5	5 34 ±3 61	>0 4

Table VII Premature ventrical beats (± standard error of the mean) per dog per minute

Group	First 5 minutes (number/min)	First 5 minutes p	Second 5 minutes (number/min)	Second 5 minutes p	Third 5 minutes (number/min)	Third 5 minutes p
1 Normal saline	5 44 ±1 44		3 09 ±1 43		2 26 ±2 09	
2 *dl* propranolol 0 1 mg/kg	4 26 ±1 18	>0 5	0 98 ±0 41	>0 1	0 70 ±0 10	>0 3
3 *dl* propranolol 1 0 mg/kg	7 87 ±2 65	>0 5	2 46 ±1 51	>0 7	0 51 ±0 22	>0 4
4 MJ 1999 0 2 mg/kg	5 27 ±1 52	>0 9	2 06 ±1 10	>0 5	4 54 ±1 78	>0 4
5 MJ 1999 3 2 mg/kg	4 47 ±1 54	>0 6	0 16 ±0 09	>0 05	0 42 ±0 32	>0 3
6 *d* propranolol 0 07 mg/kg	3 53 ±1 56	>0 3	5 17 ±3 26	>0 5	3 20 ±2 57	>0 7
7 MJ 1999 0 2 mg/kg + *d* propranolol 0 07 mg/kg	10 65 ±3 55	>0 1	6 07 ±3 82	>0 4	4 04 ±2 75	>0 5
8 AY 21 011 1 4 mg/kg	6 17 ±2 00	>0 7	0 68 ±0 34	>0 1	4 73 ±3 07	>0 5

selected for use in this study were sufficient to halve or totally inhibit the positive chronotropic response elicited by the injection of 1 5 µg per kilogram of body weight isoproterenol they were by no means adequate to block the tachycardia produced immediately following coronary occlusion in the conscious dog Yet they reduced the incidence of VF significantly The results thus suggest that the beta blocking capacity of these compounds must involve some process or processes which decreases arrhythmogenicity [27] It is well established that dl propranolol has both beta blocking and local anesthetic effects that its dextroisomer has only local anesthetic action that MJ 1999 possesses only beta blocking property and AY 21,011 is cardio selective in its action [19] It is therefore concluded from this study that cardio selective beta blockade alone is sufficient to significantly decrease the incidence of VF following experimental coronary occlusion

The number of ventricular ectopic beats occurring in trains of four or more (VT) were analyzed separately The number of ectopic ventricular beats occurring in such trains were significantly reduced ($p < 0.01$) during the first five minutes following coronary occlusion in the dogs given the lower dose of dl propranolol the higher dose of MJ 1999 the dextroisomer of propranolol alone and in combination with the lower dose of MJ 1999 It seems possible then that the local anesthetic effect of these drugs in the doses used may have contributed to the reduction of ventricular tachycardia following coronary occlusion The fact that there were more ectopic beats in the groups treated with the higher dose of dl propranolol is possibly related to the mechanism whereby quinidine like agents produce multifocal ectopic beats [8]

So many patients with coronary artery disease die suddenly (probably in ventricular fibrillation) [9,30] that the concept of precoronary care [31] has evolved The results of the present study justify further evaluation of the beta adrenergic receptor blocking drugs in experimental coronary occlusion and in carefully selected high risk individuals An analysis of the present results indicates that the choice of dose may be particularly important and that increasing the dose does not necessarily decrease the occurrence of life threatening arrhythmias

We wish to thank Dr C W Gowdey for his continuous encouragement and helpful criticism in

Table VIII Ectopic beats in the form of ventricular tachycardia per dog per minute

Group	First 5 minutes (number/min)	p	Second 5 minutes (number/min)	Third 5 minutes (number/min)
1 Normal saline	10 63 ±2 52		1 09	0
2 dl propranolol 0 1 mg/Kg	0 86 ±0 76	<0 001	0	0
3 dl propranolol 1 0 mg/Kg	3 45 ±2 83	>0 05	0	0 97
4 MJ 1999 0 2 mg/Kg	8 06 ±3 38	>0 5	2 36	0 30
5 MJ 1999 3 2 mg/Kg	0 25 ±0 19	<0 001	0	0
6 d propranolol 0 07 mg/Kg	2 98 ±1 74	<0 02	2 81	19 33
7 MJ 1999 0 2 mg/Kg + d propranolol 0 07 mg/Kg	2 36 ±0 97	<0 001	0 27	0 2
8 AY 21 011 1 4 mg/Kg	6 72 ±2 23	>0 25	0 62	0 6

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Pressure flow studies in man The nature of the aortic flow pattern in both valvular mitral insufficiency and the prolapsing mitral valve syndrome*

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As early as 1921 Wiggers and Feil[1] described the effect of acute severe mitral insufficiency on aortic blood flow in dogs Elkins and associates[2] using an electromagnetic flowmeter to record instantaneous aortic blood flow noted an abnormally high proportion of flow during the first half of ejection before mitral valve surgery in five patients with severe chronic mitral insufficiency and in nine dogs with acute mitral regurgitation Except for their work the nature of blood flow in various types of mitral insufficiency in man has not been evaluated due to the inability to measure phasic aortic blood flow The pressure gradient technique allows the investigator to estimate the instantaneous aortic blood flow in man[3] Utilizing this technique the present study was undertaken to evaluate the effects of mitral regurgitation on the pattern of instantaneous aortic blood flow in patients with mitral insufficiency secondary to either rheumatic heart disease papillary muscle dysfunction or the prolapsing mitral valve syndrome Data were obtained during a control state and following pharmacologic interventions with amyl nitrite and phenylephrine

Methods

Ten male patients and one female patient ranging in age from 41 to 56 years were studied following admission to the Durham Veterans Administration Hospital Five patients with no demonstrable cardiac disease served as the normal group In addition three patients with the classic physical angiographic and echocardiographic findings of the prolapsing mitral valve syndrome[4,5] two patients with severe mitral insufficiency secondary to chronic rheumatic heart disease and one patient with mitral insufficiency secondary to papillary muscle dysfunction were studied The clinical data describing the patients with mitral insufficiency are shown in Table 1 Cardiac catheterization was carried out on the normal subjects because of a systolic murmur and they were shown not to have mitral insufficiency or other valvular abnormalities

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Table I *Clinical data*

Patient	*Age (yr)*	*Sex*	*PA* pressure (mm Hg)*	*LA pressure (mm Hg)*	*LVEDP (mm Hg)*	*Cardiac index (L/min/M²)*
R S	42	M	22/8 (14)	(7)	10	3 0
J H	41	M	26/9 (16)	(12)	16	3 3
A W	41	F	36/15 (23)	(12)	22	2 6
M C	48	M	29/12 (18)	—	8	3 0
G G	56	M	37/15 (27)	(26)	19	3 3
O P	52	M	49/24 (40)	(37)	30	2 3

Abbreviations and symbols PA = pulmonary artery LA = left atrial LVEDP = left ventricular end diastolic pressure ECG electro WNL = within normal limits LAE = left atrial enlargement LVE = left ventricular enlargement ( ) = mean pressure
*Normal = no evidence of prolapsing valve

After informed consent was obtained, right and left sided cardiac catheterizations were performed using standard techniques Left atrial pressures were recorded through a No 2 5 Brockenbrough transseptal catheter * Cardiac outputs were measured using an indicator dilution technique Left ventricular cineangiography using 75 per cent Renografin† was carried out in all patients to determine the competency of the mitral valve Mitral insufficiency was graded as mild moderate or severe All patients with mitral valve abnormalities had selective coronary arteriograms using the Judkins technique and no lesions were seen except in the patient with papillary muscle dysfunction and posterior wall myocardial infarction The aortic valve was judged to be normal in all patients Each patient had an echocardiogram‡ examination using a 2 25 MHz one half inch diameter transducer with a repetition rate of 1 000 per second The echograms were recorded photographically directly from the oscilloscope

At the conclusion of the routine catheterization a specially designed 6 5 French Fox Fry double lumen catheter having lateral pressure taps 4 cm apart was placed percutaneously in the femoral artery and was advanced to the ascending aorta The lateral pressures were accurately measured with a transducer amplifier system* and the pressure difference was used to solve the proper equations for phasic blood flow with an analog computer† Ascending aortic pressure was simultaneously recorded from one lumen of the catheter Standard Lead II of an electrocardiogram was recorded throughout the study Continuous phasic aortic flow was then measured in each patient during a control resting state following the inhalation of amyl nitrite and also after the intravenous injection of 0 4 mg phenylephrine All data were recorded on an optical recorder‡ at a paper speed of 100 mm per second and on FM analog magnetic tape § The measurements of flow were not associated with any difficulties and the only inconvenience to the patient was the prolongation of the catheterization by approximately 30 minutes

Phasic blood flow was measured in the ascending aorta by the pressure gradient technique [3] This method is based on the solution of the Navier Stokes equations of fluid motion which relate the axial

*U S Catheter and Instrument Corp Glens Falls N Y
†E R Squibb and Sons Inc N Y
‡Ekoline 20 Mark II Echograph Smith Kline Instruments Inc Palo Alto Calif

*Model P23Db Statham Instruments Co Hato Rey Puerto Rico and Model 350 1500 Hewlett Packard Co Palo Alto Calif
†Model 3400 Donner Donner System Corp Concord Calif
‡Model 4568B Hewlett Packard Co
§Model 3955A Hewlett Packard Co

ECG	X ray	Echo	Degree of M I	Functional class (N Y H A)	Diagnosis
LAD bigeminy	WNL	Prolapsing valve	None	II	Prolapsed mitral valve syndrome
WNL	WNL	Prolapsing valve	Moderate	II	Prolapsed mitral valve syndrome
WNL	WNL	Prolapsing valve	Severe	III	Prolapsed mitral valve syndrome
Posterior infarction	WNL	Normal	Mild	II	Posterior papillary muscle dysfunction
Nonspecific T wave changes	LAE LVE calcium in mitral valve	Normal	Severe	III	Rheumatic mitral insufficiency
LAD LAE LVE	LAE LVE calcium in mitral valve	Normal	Severe	III	Rheumatic mitral insufficiency

...diogram Echo = echocardiogram M I = mitral insufficiency N Y H A = New York Heart Association LAD = left axis deviation

pressure gradient to the flow The details concerning calibration to obtain flow with this technique have been described elsewhere[5] and the validity has been demonstrated in a flow generator in the dog aorta and in man[5,7,8]

The average values obtained from 10 heart beats in each situation were computed Stroke volume (cm^3) was obtained by the planimetric integration of the total area under each flow curve The flow curve was divided into two equal parts as a function of time and the flow during each part was determined and expressed as a per cent of total stroke volume (Fig 1) Peak flow (cm^3 per second) was measured as the maximum value directly from the flow curve The systolic and diastolic aortic blood pressures (mm Hg) were obtained directly from the record and the mean pressure was computed

Results

In Table II are listed the hemodynamic parameters for each patient with mitral insufficiency and the mean values for the normal patients Typical flow curves from one normal and from two patients with the various types of mitral regurgitation in the control state and with each pharmacologic intervention are shown in Fig 1

The five patients with normal mitral valves had blood flow curves during control and following phenylephrine in which the per cent flow was approximately evenly divided between the first and second halves of ejection Inhalation of amyl nitrite resulted in a greater per cent of flow during the first half of ejection

The proportion of aortic blood flow ejected during the first half of systole in patients with the prolapsing mitral valve syndrome was related to the presence of mitral regurgitation In the patient (R S) with a prolapsing mitral valve but without mitral insufficiency the blood flow curves were similar to the normal individuals However in the two patients with mitral regurgitation (J H and A W) the per cent of flow in the first half of ejection was markedly increased during the control state In these two patients following amyl nitrite and phenylephrine administration the aortic flow during the first half of ejection tended to decrease

The three patients with either rheumatic mitral insufficiency or papillary muscle dysfunction had a greater proportion of flow during the first half of ejection during control This augmentation of early systolic flow persisted following amyl nitrite and phenylephrine

Discussion

The finding of an approximately evenly divided percentage of aortic flow in the first and second halves of ejection in patients with competent mitral valves is in

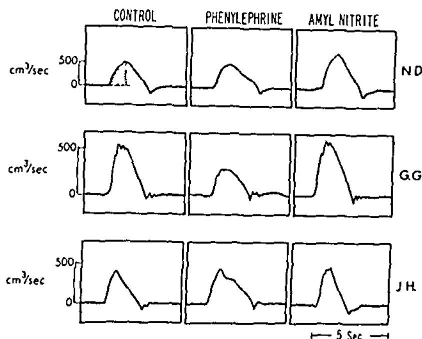


Fig *1* Representative aortic flow curves obtained during the control state following inhalation of amyl nitrite *and the intravenous injection of 0.4 mg phenylephrine N D is normal C G has rheumatic mitral insufficiency* and *J H* has moderate mitral insufficiency secondary to a prolapsing mitral valve The stippled area illustrates the flow during the first half of ejection

keeping with the previous reports from this laboratory[7,9] and the work of Elkins and associates[2] following mitral valve replacement It should be noted that in our normal patients the range of stroke volumes was quite variable but the per cent of flow in the first half of ejection was consistent from patient to patient during both the control and following administration of amyl nitrite and phenylephrine Previous data from our laboratory have shown that the proportion of flow during the first half of ejection is not related to the magnitude of the stroke volume[7] Inhalation of amyl nitrite by normal individuals decreases mean aortic blood pressure and increases cardiac output by increasing stroke volume with little effect on heart rate[10] These effects are associated with a greater per cent of aortic blood flow during the first half of ejection (Fig 1) A possible explanation for the phenomenon is that the lower aortic impedance to flow allows a rapid initial ejection resulting in an "empty ventricle during the latter part of systole Thus, during the second half of ejection the proportion of flow is reduced This finding is somewhat analogous to the patients with hypertrophic subaortic stenosis in whom an increase in per cent of flow in the first half of ejection occurs in the control state possibly due to excessively rapid emptying[9] In addition, the decrease in arterial pressure may evoke a release of catecholamines which could result in an increase in myocardial contractility and would augment the ejection during early systole Phenylephrine usually produces bradycardia a rise in blood pressure and a decrease in stroke volume These hemodynamic responses in our normal patients were not marked and the contour of flow curves remained essentially unchanged

An abnormal pattern of instantaneous aortic blood flow during the control state was demonstrated in each of the patients with mitral insufficiency due to either rheumatic disease or papillary muscle dysfunction in that the per cent of aortic flow is higher during the first half of ejection than in the normal subjects (Fig 1) Similar findings were reported by Elkins and associates[2] who measured aortic blood flow in five human subjects with an electromagnetic flowmeter before and after mitral valve replacement These workers found 65 per cent of the flow to occur in the first half of ejection prior to the valve replacement and 50 per cent postoperatively One possible explanation for the finding is that the dilatation of the heart seen in these patients augments the contractile ability of

Table II Hemodynamic data

Patient		Stroke volume (cm³)	Peak flow (cm³/sec)	Heart rate (beats/min)	Mean aortic blood pressure (mm Hg)	Flow first half ejection (%)
R S	(C)	64	590	75	95	48
(LMV)	(P)	83	536	62	119	45
	(AN)	61	580	85	86	55
J H	(C)	60	420	82	109	68
(LMV)	(P)	75	450	61	120	63
	(AN)	49	450	109	95	57
A W	(C)	55	390	62	132	66
(PMV)	(P)	52	300	60	158	59
	(AN)	62	480	73	98	61
M C	(C)	52	290	85	104	64
(PD)	(P)	65	340	86	114	61
	(AN)	50	323	100	84	61
G G	(C)	56	500	97	114	58
(RMI)	(P)	42	360	99	138	56
	(AN)	60	540	99	103	59
O I	(C)	27	230	97	77	59
(RMI)	(P)	18	180	92	90	57
	(AN)	31	250	96	61	57
Normal	(C)	53 ± 11	340 ± 58	84 ± 13	101 ± 9	52 ± 1
	(P)†	38 ± 11	380 ± 57	79 ± 14	107 ± 9	52 ± 2
	(AN)	76 ± 18	490 ± 89	86 ± 11	73 ± 10	60 ± 2

Tl m ± t d d f th me e l t d f r tl fi mal p t e t
†D t bt ed th ee t tient
Abb t (C) = o t l (P) = phe yleph ne (AN) = myl n t t PMV = p l p g m t al al PD = p p ll y muscl dysf t RMI = h m tic m tral uffic cy

the heart secondary to the Frank Starling mechanism During the initial part of ejection the flow is increased but as ejection proceeds the volume of the heart decreases markedly due to the large total stroke volume thus during the latter part of ejection the heart cannot maintain this augmented rate of ejection The observations of Ross and associates[11] would tend to substantiate this hypothesis In these patients the inhalation of amyl nitrite has little effect on the per cent of aortic flow during the first half of ejection because a nearly maximal rate of flow for the patient has already been achieved in the control state for the reasons outlined above The decreased aortic impedance under these circumstances did increase the aortic flow and may have reduced the amount of regurgitation but had little effect on the percentage of flow occurring in the first half of ejection Phenylephrine did not change the percentage of aortic flow in the first half of ejection although undoubtedly the total degree of mitral insufficiency was increased

Late systolic murmurs accompanied by systolic clicks are frequently seen in the prolapsing mitral valve syndrome and are usually associated with mitral insufficiency[4,12,17] Provocative studies have shown that the late systolic murmur becomes more pansystolic and softer with amyl nitrite and louder without change in systolic timing with pressor amines[15] The clicks associated with the syndrome often become softer with amyl nitrite and louder with pressor amines Echocardiography reveals the prolapse of the posterior leaflet of the mitral valve to occur earlier in systole following amyl nitrite[18] Cineangiographic data reveal earlier and increased mitral

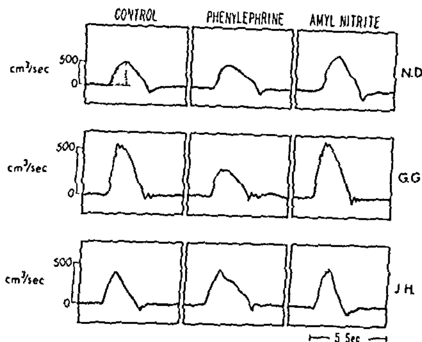


Fig. 1. Representative aortic flow curves obtained during the control state following inhalation of amyl nitrite and the intravenous injection of 0.4 mg. phenylephrine. N.D. is normal, G.G. has rheumatic mitral insufficiency, and J.H. has moderate mitral insufficiency secondary to a prolapsing mitral valve. The stippled area illustrates the flow during the first half of ejection.

keeping with the previous reports from this laboratory[7,9] and the work of Elkins and associates[2] following mitral valve replacement. It should be noted that in our normal patients the range of stroke volumes was quite variable, but the per cent of flow in the first half of ejection was consistent from patient to patient during both the control and following administration of amyl nitrite and phenylephrine. Previous data from our laboratory have shown that the proportion of flow during the first half of ejection is not related to the magnitude of the stroke volume.[7] Inhalation of amyl nitrite by normal individuals decreases mean aortic blood pressure and increases cardiac output by increasing stroke volume with little effect on heart rate.[10] These effects are associated with a greater per cent of aortic blood flow during the first half of ejection (Fig. 1). A possible explanation for the phenomenon is that the lower aortic impedance to flow allows a rapid initial ejection resulting in an "empty ventricle" during the latter part of systole. Thus during the second half of ejection the proportion of flow is reduced. This finding is somewhat analogous to the patients with hypertrophic subaortic stenosis in whom an increase in per cent of flow in the first half of ejection occurs in the control state possibly due to excessively rapid emptying.[9] In addition, the decrease in arterial pressure may evoke a release of catecholamines which could result in an increase in myocardial contractility and would augment the ejection during early systole. Phenylephrine usually produces bradycardia, a rise in blood pressure, and a decrease in stroke volume. These hemodynamic responses in our normal patients were not marked and the contour of flow curves remained essentially unchanged.

An abnormal pattern of instantaneous aortic blood flow during the control state was demonstrated in each of the patients with mitral insufficiency due to either rheumatic disease or papillary muscle dysfunction in that the per cent of aortic flow is higher during the first half of ejection than in the normal subjects (Fig. 1). Similar findings were reported by Elkins and associates[2] who measured aortic blood flow in five human subjects with an electromagnetic flowmeter before and after mitral valve replacement. These workers found 65 per cent of the flow to occur in the first half of ejection prior to the valve replacement and 50 per cent postoperatively. One possible explanation for the finding is that the dilatation of the heart seen in these patients augments the contractile ability of

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insufficiency secondary to amyl nitrite.[19]

Patient R. S. had a prolapsing posterior leaflet of the mitral valve as proved by cineangiography and echocardiography but no mitral insufficiency could be seen with angiography. His control aortic flow curves and the responses to both amyl nitrite and phenylephrine were similar to the normal patients. J. H. and A. W. were patients with the prolapsing mitral valve syndrome having moderate and severe mitral insufficiency respectively. During the control state, the percentage of flow during the first half of ejection was even more increased in these patients than in the other patients with mitral insufficiency. It is probable that the previously described factors which are responsible for the increase in flow during the first half of ejection in mitral insufficiency also operate in these patients. In addition, since regurgitation across the mitral valve begins later during systole, the percentage of aortic flow during the first half of ejection would be further enhanced. An increase in mitral regurgitation during the latter part of systole may also have been present in our patient with papillary muscle dysfunction and may account for the finding of higher proportions of flow during the first half of ejection than in the patients with rheumatic disease. In the two patients with prolapsing mitral valves the inhalation of amyl nitrite resulted in a decrease in the per cent of aortic flow during the first half of ejection. Presumably this was due to the occurrence of mitral insufficiency earlier during systole than in the control state as evidenced by the echocardiographic and phonocardiographic findings described above. The reason for the decrease in the per cent of aortic flow during the first half of ejection following phenylephrine administration in these two patients is not immediately apparent. The increased aortic impedance to flow following the drug may result in dilating the left ventricle. This in turn may make the prolapsing valve less insufficient during the latter part of ejection.

Summary

In five normal patients and in six patients with various forms of mitral insufficiency, ascending aortic pressure flow relationships were studied using the pressure gradient technique. Stroke volume, peak flow, mean aortic pressure, and the per cent of aortic flow during the first half of ejection were calculated in the control state, following amyl nitrite inhalation, and following the intravenous injection of 0.4 mg. of phenylephrine. In normal patients an average of 52 per cent of flow occurred in the first half of ejection both during control and following phenylephrine and increased to 60 per cent after amyl nitrite. A patient with the prolapsing mitral valve syndrome but without mitral insufficiency had flow curves similar to the normal. Two patients with moderate and severe mitral insufficiency, respectively, and a prolapsing mitral valve had a marked increase in flow during the first half of ejection (68 and 66 per cent) during control; the per cent of flow decreased with amyl nitrite and phenylephrine administration. Patients with mitral insufficiency secondary to either rheumatic heart disease or papillary muscle dysfunction had 58 to 64 per cent of flow during the first half of ejection during control; this pattern did not change significantly with amyl nitrite or phenylephrine.

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Anodal stimulation as a cause of pacemaker-induced ventricular fibrillation

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The possibility of pacemaker-induced ventricular arrhythmias has been recognized since the beginning of widespread use of artificial pacemakers,[1-18] but the extent of the clinical risk of such arrhythmias has been questionable.[17, 8] The possibility of a dangerous arrhythmia being precipitated by a pacemaker stimulus falling during the vulnerable period of a preceding ventricular beat exists most commonly when an asynchronous artificial pacemaker is in competition with normal sinus rhythm or ectopic beats from any source. The risk is particularly great in patients requiring pacing during acute myocardial infarction, as these patients are most susceptible to life-threatening ventricular arrhythmias.[18, 20, 26, 27, 28, 30, 33] This is a review of the reported studies of pacemaker-induced ventricular arrhythmia with attention to the type of electrodes used, unipolar or bipolar. Every documented case of pacemaker-induced ventricular tachycardia or fibrillation occurred in association with a bipolar electrode system, adding support to the concept that these arrhythmias are evoked at the anode and do not occur with unipolar cathodal pacing.

Methods

A survey was made of all reported instances of ventricular tachycardia or fibrillation occurring in human patients with artificial ventricular pacemakers. The events were separated into two categories: (1) documented episodes in which the onset of the ventricular arrhythmia followed a pacemaker stimulus falling during the vulnerable period of the preceding beat, and (2) episodes in which the ventricular arrhythmia but not its onset was documented. There are in addition reports of pacemaker-induced ventricular arrhythmia in which the arrhythmia was not documented[6, 1, 13, 20, 34, 3] or in which the electrode configuration was not stated.[34, 36, 37, 4] For the purposes of this study a ventricular arrhythmia was defined as four or more responses following a pacemaker stimulus. The stimulus was judged to fall in the vulnerable period if it occurred during the T wave of the preceding beat.

Each case was further categorized as bipolar or unipolar stimulation, with the assumption that in all cases of unipolar pacing the intracardiac electrode was the cathode and the indifferent electrode was the anode. Although it is possible to re-

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Table I Documented onset of pacemaker induced ventricular tachycardia or ventricular fibrillation in humans

	Electrode system	No of patients	Arrhythmia
Bertrand[1]	Bipolar	1	VF
Bilitch[25]	Bipolar	1	VF
Castellanos[30]	Bipolar	1	VF
Elmqvist[6]	Bipolar	1	VF
Fletcher[4]	Bipolar	2	1 VT 1 VF
Grondin[7]	Bipolar	1	VT
Jensen[5]	Bipolar	1	VT
Julian[23]	Bipolar	4	VF
Kleiger[7]	Bipolar	1	VT
Lemberg[25]	Bipolar	2	1 VT 1 VF
Preston[12]	Bipolar	2	VF
Robinson[4]	Bipolar	1	VF
Roe[33]	Bipolar	1	VF
Tavel[3]	Bipolar	1	VF
Weinberg[17]	Bipolar	1	VT

Abbreviations VT = ventricular tachycardia VF = ventricular fibrillation

verse polarity in external pacing all commercially available permanent implant pacemakers which are unipolar are fixed with anodal stimulation at the indifferent electrode

Results

In every case of documented onset of ventricular tachycardia or ventricular fibrillation (21 cases) with the pacemaker stimulus falling in the vulnerable period of the preceding beat the electrode system employed was bipolar (see Table I) We were unable to find such a case using a unipolar system Sowton and Flores[17 18] have reported two patients who developed ventricular fibrillation shortly after receiving permanent unipolar pacemakers which competed with normal sinus rhythms In the first patient the onset was not documented although the author considered it to be pacemaker induced He does state however because there is no written ECG record it is just possible that the whole sequence was due to the spontaneous onset of ventricular fibrillation [18] Sowton s second case was also undocumented and although the patient was found with ventricular fibrillation the episode was apparently preceded by abdominal distention vomiting and aspiration In a patient reported by Roe and Katz [33] unipolar pacing did not result in a ventricular arrhythmia whereas bipolar pacing in the same patient resulted in recurrent bouts of ventricular fibrillation Of the 21 episodes of pacemaker induced ventricular tachycardia there were no reported episodes of ventricular arrhythmia arising from a pacemaker stimulus falling outside the vulnerable period

There were 34 episodes of ventricular tachycardia or ventricular fibrillation documented in patients with functioning artificial pacemakers but without documentation of the onset of the arrhythmia [2 3 6 8 10 11 14 17 18 21 23 29] In 33 patients the pacemaker was operating as a fixed rate (competitive) type and one patient had a normally functioning demand (noncompetitive) unit Twenty-eight episodes were with bipolar electrodes and six episodes were with unipolar electrodes Thirty episodes were ventricular fibrillation four episodes were ventricular tachycardia

Discussion

The problem of pacemaker induced ventricular tachycardia or ventricular fibrillation has been studied since pacemakers have been in common use Most reports stress the improbability of this phenomenon but some notable exceptions have been documented Sowton[3] in 1965 reported six patients who developed ventricular tachycardia or ventricular fibrillation while in parasystole with sinus rhythm

and a non inhibited fixed rate pacemaker and concluded that especially in the first two days after implantation there is a risk of pacemaker induced ventricular arrhythmia Bilitch and co workers[33] reported a case of ventricular fibrillation occurring in a patient who had an acute myocardial infarction with documentation of the onset of the arrhythmia at the time of a pacemaker stimulus falling in the vulnerable period of the preceding beat Castellanos and co workers[50] studied 14 human patients and were able to produce repetitive firing in three patients and ventricular fibrillation in one patient by scanning the vulnerable period with bipolar right ventricular pacing Welti and colleagues[40] also produced repetitive firing in humans by scanning the vulnerable period with bipolar stimuli of low amplitude Lewis and associates[41] using unipolar pacing were unable to produce ventricular arrhythmias

Clinical studies comparing groups of patients with competitive and noncompetitive systems have yielded conflicting conclusions Furman and colleagues[5] report no increased incidence of sudden death in patients with non triggered or competitive units while Bilitch[18] reported death due to ventricular fibrillation in 5 of 40 patients with fixed rate units and only one death due to ventricular fibrillation in 46 patients with demand units Most investigators feel that pacemaker induced ventricular arrhythmias are most likely during acute myocardial infarction[19, 20, 24, 26, 42] during the first two days after implantation of the electrodes[3, 3] or during periods of hypoxia[4, 27] or electrolyte imbalance[24, 27] Another example of ventricular arrhythmia produced by pacing during the vulnerable period is that of paired pacing of the ventricle Bipolar electrodes are almost always employed for paired pacing and similarly the complication of ventricular tachycardia and fibrillation has been associated with bipolar not unipolar, electrode systems[40, 43, 50]

The results shown in Table I suggest an association of pacemaker induced ventricular fibrillation with bipolar electrodes in the human There is no documented case of human pacemaker induced ventricular tachycardia or ventricular fibrillation with unipolar electrodes although unipolar systems probably account for almost half of all implanted pacemakers

Although the cardiac electrode of a permanent unipolar system is connected to the cathode of the impulse generator in temporary systems it is possible to connect the cardiac electrode to the anode of the impulse generator in which case the risk of anodal pacing would be the same as for a bipolar system This could have been the situation in the two patients reported by Portal and colleagues[7] and in other cases of temporary unipolar pacing One of two patients reported by Crondin and co workers[74] had a unipolarized electrode system with repetitive firing but whether anode or cathode was made the indifferent electrode is not known

Some patients with artificial pacing will develop ventricular arrhythmias not induced by a pacing stimulus For this reason only the documented onset of pacemaker induced ventricular tachycardia or ventricular fibrillation is acceptable as evidence of association with the electrode system in use at the time of the arrhythmia

Numerous investigators have studied induction of ventricular arrhythmias in animals by repetitive firing during the vulnerable period Most investigations have been carried out with bipolar electrodes[51, 54, 56, 59, 61, 66, 70] with fewer studies of fibrillation thresholds with unipolar cathodal or anodal stimulation[19, 55, 60, 62, 63] In studies comparing anodal and cathodal stimulation experimental evidence consistently demonstrated increased vulnerability to ventricular arrhythmias from anodal as compared to cathodal stimulation[42, 55, 60, 64, 65] Chardack and colleagues[19] using unipolar *cathodal* stimulation were unable to increase the prevalence of ventricular fibrillation in dogs with acute coronary occlusion Although this was taken as evidence of the safety of artificial pacing it is possible that the low prevalence of fibrillation was associated with the absence of anodal stimulation

Hoffman and Cranefield[64] concluded that during induction of ventricular fibrillation with bipolar electrodes the ventricular fibrillation is initiated at the anode They state 'If the flow of anodal current is sufficiently diffuse it is so difficult to evoke fibrillation that it seems safe to assume that fibrillation evoked by electrical stimulation depends upon anodal

Cranefield and associates[5] ruled out a double origin of ventricular fibrillation from both the anode and cathode and concluded that the vulnerable period coincides with the period when threshold excitation occurs at the anode

Conclusions

The association of bipolar electrodes in humans and animals with pacemaker induced ventricular arrhythmias suggests that in the majority of instances an anode on or within the heart of size and configuration to permit anodal stimulation is necessary to produce ventricular tachycardia or ventricular fibrillation in humans with permanent or temporary pacing systems As excitation during the vulnerable period is usually possible only at the anode[64,65] with the excitation threshold often ten times as great at the cathode it does seem likely that single responses during the vulnerable period are usually evoked at the anode with presently used human pacing systems It follows that the origin of repetitive ventricular beats or ventricular fibrillation is equally likely to be at the anode

Evidence is lacking that pacemaker induced arrhythmias are common and commercially available pacemakers have outputs which are probably too small to produce arrhythmias in *normal* human hearts It is probable that with impulse durations of one msec or less as is now common with commercial units it is almost impossible to produce arrhythmias due to pacing in the vulnerable period[3] However commercial units must be designed to produce stimuli exceeding the excitation thresholds of 95 per cent or more of all patients encountered With time the excitation threshold for an implanted electrode system can rise to 10 times the initial implantation threshold and therefore pacemakers are designed to deliver 10 to 30 times as great a stimulus as is required for effective pacing at the time of electrode implantation Therefore under adverse conditions which lower the fibrillation threshold such as acute myocardial infarction hypoxia electrolyte imbalance or during the first two days after implantation pacemaker induced ventricular arrhythmias are possible especially if the anode is on or inside the ventricle

The use of demand (noncompetitive) pacemakers has reduced the frequency with which pacing stimuli fall in the vulnerable period of the preceding beat but demand type pacemakers are not totally reliable for this purpose as they are subject to failure or outside interference in which case they perform as fixed rate units Especially with bipolar electrodes even a normally functioning demand pacemaker may fail to sense some spontaneous beats resulting in competitive pacing

The coronary care unit is a high risk area for pacemaker induced ventricular arrhythmias because of the higher prevalence of ectopic beats which are not sensed by demand pacemakers and the markedly reduced fibrillation threshold of patients with acute myocardial infarction Therefore in the coronary care unit only unipolar cathodal pacing should be used As most pacing in a coronary care unit is through temporary catheter electrodes either a remote indifferent electrode (anode) or a catheter with a distal pacing electrode (cathode) and a large proximal electrode (anode—at least ten times the surface area of the distal electrode) positioned outside of the right ventricle should be used Virtually all temporary endocardial pacing systems employ bipolar electrodes and bipolar pacemakers such that the pacemaker anode can be attached to either electrode Elimination of bipolar temporary systems should increase the safety of temporary pacing

Although the danger of pacemaker induced ventricular arrhythmia exists mostly in patients with hypoxia or acute myocardial infarction the greater possibility of such arrhythmias with bipolar electrodes in any situation militates against the general use of bipolar electrodes

Summary

A review of animal investigations suggests that pacemaker induced ventricular fibrillation usually occurs at the anode and in fact is difficult to evoke at the cathode A search of the literature showed that every documented episode of pacemaker induced ventricular tachycardia/fibrillation in humans has been with a bipolar electrode system Since the problem most often occurs during temporary pacing associated with myocardial infarction bi

and a non-inhibited fixed-rate pacemaker and concluded that especially in the first two days after implantation there is a risk of pacemaker-induced ventricular arrhythmia. Bilitch and co-workers[33] reported a case of ventricular fibrillation occurring in a patient who had an acute myocardial infarction with documentation of the onset of the arrhythmia at the time of a pacemaker stimulus falling in the vulnerable period of the preceding beat. Castellanos and co-workers[50] studied 14 human patients and were able to produce repetitive firing in three patients and ventricular fibrillation in one patient by scanning the vulnerable period with bipolar right ventricular pacing. Welti and colleagues[40] also produced repetitive firing in humans by scanning the vulnerable period with bipolar stimuli of low amplitude. Lewis and associates[41] using unipolar pacing were unable to produce ventricular arrhythmias.

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polar catheter electrodes should not be used for temporary pacing, and the use of unipolar (cathodal) pacing systems should increase the safety of electrical pacing

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The value of warning arrhythmias in the prediction of ventricular fibrillation within one hour of coronary occlusion Experimental studies in the baboon*

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Sudden death in acute myocardial infarction is generally held to be the result of ventricular fibrillation [1] In acute myocardial infarction the vulnerable period (or descending limb of the T wave) is prolonged and the ventricular fibrillation threshold is decreased both favoring the development of ventricular fibrillation [2,3] Primary ventricular fibrillation in acute myocardial infarction has its peak incidence in the first hour and decreases progressively in the next hour and sudden death is the first symptom of ischemic heart disease in 20 to 25 per cent of cases [4,5] Of 596 patients with acute myocardial infarction who were not admitted to hospital 75 per cent died within 2 hours of the attack [6] A one year survey in the Edinburgh area showed 73 per cent of all deaths occurring within 4 weeks of acute myocardial infarction occurred outside the hospital and 45 per cent of all deaths occurred within 1 *hour of the onset of* an acute attack [7] Thus to investigate the majority of cases of ventricular fibrillation occurring in acute myocardial infarction requires continuous monitoring of the rhythm in the first hour of the heart attack

However the average time interval between the onset of illness and admission to the majority of Coronary Care Units is between 6 and 9 hours [6,8,11] Even the fastest mobile Coronary Care Units cannot reach the patient until 20 to 30 minutes have elapsed These delays explain why many publications on primary ventricular fibrillation in acute myocardial infarction lack information about the first few hours after the onset of the infarction and why there is a controversy about the nature and incidence of warning arrhythmias preceding primary ventricular fibrillation in acute myocardial infarction Thus the investigation of the incidence of ventricular fibrillation in the first hour of acute myocardial infarction and the identification of warning arrhythmias requires an animal model We studied a subhuman primate (the Cape Chacma baboon) which we believe provides a better model of the arrhythmias associated with human myocardial infarction than does the dog [15]

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cotomy was performed without coronary artery ligation In one of these a coronary artery was dissected but was not ligated

Blood samples The right femoral artery was cannulated and the first blood sample was taken within 30 minutes after the Sernylan injection and before the start of artificial respiration Thereafter samples were taken throughout the experimental period before and after the production of the infarct

The initial and final value of pH and Pco_2 of all baboons included were within the physiological range and did not differ The hemoglobin and hematocrit in male baboons were initially 14 7 Gm per 100 ml and 44 per cent and decreased by the end of the experiment by 0 6 Gm per 100 ml and 2 per cent respectively The hemoglobin and hematocrit in the female baboons were initially 13 8 Gm per 100 ml and 41 5 per cent and decreased at the end of the experiment by 1 19 Gm per 100 ml and 4 per cent respectively The greater blood loss in females was due to more prolonged bleeding from the cut sternum The initial plasma K^+ was 3 9 ± 0 1 mEq per liter which fell by an average of 0 5 mEq per liter during the total period of anesthesia and muscle immobilization which lasted 2 to 3 hours There was no significant change between the initial and final values of blood enzymes and free fatty acids in all animals An infusion of 4 5 Gm per liter NaCl was started in 15 baboons 3 minutes after the production of the infarct at an average rate of 0 200 ml per kilogram of body weight per minute until the end of the first hour of observation In 25 other baboons with infarct no infusion was given during the whole experiment Of the 10 control baboons 5 received 4 5 Gm per liter NaCl during the first hour and 5 received none The infusion fluids were preheated to body temperature

Size of infarction The size of the infarct or the area of the ventricle supplied by the ligated coronary artery was defined by the appearance of a dark brownish blue zone with a sharp edge and marked ST elevation on the epicardial electrocardiogram[2] At the end of the experiment a transmural cut was made along the clearly defined edge and the infarct was weighed in the wet state The size was calculated as the percentage of the total wet heart weight cut 1 cm above the semilunar valves The infarct area was always transmural and the size was confirmed afterwards by biochemical changes in the tissue (loss of high energy phosphate compounds glycogen and potassium/sodium ratio) and very low coronary blood flow as measured by injections of microspheres labeled with isotopes[21]

Site of infarction The situation of the infarct was anterolateral when the proximal third of the main diagonal branch of the left coronary artery was ligated (Fig 1) This artery corresponds to the description of the third primary division of the left coronary artery in the baboon[22] Ligation of the mid third or distal third part of the anterior descending coronary artery resulted in an anteroseptal infarct also involving the apex Ligation of the mid third or distal third part of the circumflex coronary artery produced a posterior infarct An inferoposterior infarct was obtained by a double ligation of the distal third of the anterior descending and circumflex coronary artery The right coronary artery and proximal third of the anterior descending and circumflex coronary artery were never tied

Electrocardiographic monitoring Four needle tipped electrodes of an electrocardiogram recorder (Corbin Farnsworth 55EP deluxe scopette with dual trace control with direct graphic recorder ECCR) were connected subcutaneously to the appropriate limbs A standard lead (III or aV_F) was continuously recorded at 5 or 25 mm per second throughout the experiment (1 mV = 1 cm) In the same experiments a tape recorder (Holter System Avionics) was connected by 3 hypodermic needles to the chest for a second continuous recording because the direct writer was intermittently used to record the epicardial electrocardiograph

Definitions of warning arrhythmias The following arrhythmias were chosen retrospectively after they appeared to be most frequently associated with ventricular fibrillation R on T phenomenon was defined as a ventricular ectopic beat appearing in the descent of the T wave of a sinus beat or of another ventricular ectopic beat[10,14,23,24]

Material and methods

Animals Fifty apparently healthy, wild living Cape Chacma baboons (*Papio Ursinus*) were used for the experiments within 1 or 2 weeks after being captured in their natural surroundings Forty two were males with an average body weight of 23 5 ± 0 5 kilograms (mean ± SEM, range 14 to 32 kilograms) and eight females with an average body weight of 15 ± 1 kilogram (range 9 to 20 kilograms) The ratio of body weight to heart weight was 198 ± 5 (5 17 ± 0 12 Gm heart tissue per kilogram of body weight) with no significant difference between females and males The use of the same variety of baboon throughout made it possible to estimate the age by the following criteria

1 BODY WEIGHT Adolescent male and female baboons had a body weight of less than 21 kilograms and 14 kilograms, respectively adult and old baboons exceeded these weights

2 TEETH Adolescent male and female baboons had permanent teeth which were small with no signs of wear no teeth were lacking The teeth of adult baboons were long especially the canines When teeth were lacking excessively worn or diseased these baboons were considered to be old

3 BLOOD ALKALINE PHOSPHATASE The alkaline phosphatase of adolescent baboons was 584 ± 33 I U per milliliter (n = 9) Adults and old baboons had an alkaline phosphatase value of 197 ± 23 I U per milliliter (n = 41 p < 0 0005)

4 EPICARDIAL FAT AND CORONARY ARTERIES When the chest was opened there was generally more yellow epicardial fat in older baboons and their coronary arteries were tortuous Adolescent baboons were considered to be less than 7 years of age "adult" baboons between 8 and 20 years of age, and old baboons between 20 to 30 years[18]

Baboons were starved overnight prior to the experiment and received no antibiotic antituberculous or antiparasitic treatment nor any other drugs

Anesthesia and respiration Phencyclidine HCl (Sernylan) 1 25 mg per kilogram of body weight was used to paralyze and to initiate anesthesia which was maintained by intermittent intravenous doses of 30 to 60 mg of pentobarbital (average rate of administration 0 06 ± 0 003 mg per kilogram of body weight per minute) The baboon was intubated, connected to a Harvard respirator pump (model 607) and ventilated with room air at a fixed rate of 16 strokes per minute against a constant end expiratory pressure of 5 cm water[17,19] The stroke volume checked by arterial Astrup readings was about 7 ml per kilogram of body weight Initial Po_2 was 73 ± 3 mm Hg and the final Po_2 was 82 ± 6 mm Hg (11 baboons)

Operative procedure With the baboon lying supine, the chest was opened by mid sternal thoracotomy and the heart was suspended in a pericardial cradle after incision of the pericardium parallel to the phrenic nerve The baboon was turned over to an angle of 45 degrees in the left anterior oblique position for the remainder of the experiment

The room temperature was kept at about 30° C throughout the whole experiment by electrical fan heating The body temperature was checked with a thermocouple electrode in the esophagus The average body temperature was 37 5° C in males and 38° C in females and decreased by about 0 5° C by the end of the experimental period

No antiarrhythmic drug analgesic drug heparin or oxygen was administered during the experiment

Production of myocardial infarction One or two branches of the left coronary artery were dissected from their veins and ligated with a linen thread Within 1 minute of ligation a dark brownish blue epicardial area with a very sharply defined edge appeared In the next hour of observation the color difference between ischemic and non ischemic tissue became more marked but no visible change in the size of the infarct occurred Depending on the size and site of the infarct bulging of the ischemic free wall of the left ventricle occurred during systole

Our aim was to produce a single infarct of about 10 per cent of the total wet heart weight In 34 baboons one ligation of a coronary artery was sufficient but in 6 others 2 contiguous areas supplied by different coronary artery branches had to be tied depending on the anatomy of the coronary arteries In 10 baboons a thora

Table I. Correlation of size of infarct, sex, age, and mortality rate

	Male		*Female*	
	Survival	*V.F.*†	*Survival*	*V.F.*
Adolescent‡ ≤7 years	2	2	1	0
Adult 8-20 years	7	19	3	2
Old 20-30 years	0	2	0	0
Total number	9	23	4	2
%	28	72	66	34
Average size infarct (Mean ± SEM)	7 ± 1%§‖	12 ± 1%§	11 ± 1%‖	12 ± 6%

Survival = No V.F. within 60 minutes.
†V.F. = Ventricular fibrillation within 60 minutes of coronary artery ligation.
‡Age groups as defined in text.
§ = p value < 0.005 for significance of comparison.
‖ = p < 0.05.

Table II. Correlation between size and site of infarction and incidence and interval between arterial ligation and development of ventricular fibrillation (V.F.)

	Anterolateral infarct		*Anteroseptal infarct*		*Posterior infarct*		*Inferoposterior infarct*	
	V.F.	*Survival*	*V.F.*	*Survival*	*V.F.*	*Survival*	*V.F.*	*Survival*
Number of baboons	7	0	11	8	4	5	3	1
Size of infarct	17	—	10	11	9	5	12	11
(Mean ± SEM)	± 7	—	± 2	± 1	± 2	± 0.5	± 2	
Minutes after ligation	31	—	35	60	50	60	23	60
(Mean ± SEM)	± 2	—	± 4		± 7		± 8	
% developing V.F.	100		58		44		75	

Abbreviations as in Table I.

to the development of ventricular fibrillation. In 3 adolescent baboons with infarction, 2 baboons developed V.F. In 31 adult baboons, 21 developed V.F. In 2 old baboons, both developed V.F. (Table I). Sex was also related to the development of V.F. Of 6 female baboons with infarction, 2 developed V.F. Of 32 male baboons, 23 developed V.F. These findings correspond well with the correlation of mortality rate with sex and increasing age in humans with acute myocardial infarction.[8,10,22,23] The control baboons consisted of 8 males (2 adolescent, 5 adult, 1 old, with mean body weight of 24.3 ± 1.7 kilograms) and 2 females (1 adolescent, weight 12.3 kilograms, and 1 adult of 18 kilograms).

The size of the infarct was particularly important for male survival and a 10 per cent infarct was the critical size in this group. The average size of the infarct of the males who developed V.F. was significantly larger (p < 0.005) than of the males who survived.

The *female* group who survived had a larger infarct than the male survival group (p < 0.05). Although some subgroups are rather small, it is likely that increasing age and size of infarction increased the incidence of V.F. *for male baboons*. Females

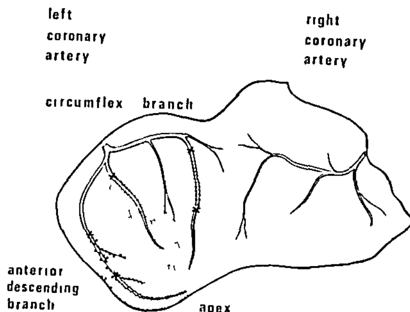


Fig. 1. Schematic representation of the free wall of the left and right ventricle spread open. The shaded areas on the left side correspond to the infarction areas produced by ligation of the mid and distal third portions of the descending coronary branch. The shaded areas on the right side correspond to the infarction areas produced by ligation of the mid and distal third portions of the circumflex coronary branch. The shaded area in between corresponds to the infarction area produced by ligation of the proximal third of the main diagonal branch (third primary branch[23]).

R on T beats initiating ventricular tachycardia or ventricular fibrillation were not included as a warning arrhythmia. Ventricular bigeminy was defined as the alternation of a sinus beat and a premature ventricular ectopic beat for at least 4 consecutive beats.[25] Ventricular tachycardia was defined as 3 or more unifocal or multifocal consecutive ventricular ectopic beats at a rate of more than 140 per minute.[2, 14, 25, 6] Short bursts as well as long runs were included. Ventricular tachycardia which initiated ventricular fibrillation was not included. Occasional arrhythmias occurring during the intermittent recording of the electrogram with the handheld epicardial electrode were discarded.

The method of prediction of imminent ventricular fibrillation in the presence of acute myocardial infarction was based on the first and last appearance time of the above three arrhythmias. The first appearance time was defined as the time interval between the beginning of the first occurrence of the arrhythmia after coronary artery ligation and the end of the experiment. The last appearance time was defined as the time interval between the beginning of the last occurrence of the arrhythmia (before the end of the experiment) and the end which was onset of ventricular fibrillation or the 60th minute after coronary artery ligation.

Discarded experiments. Two baboons in whom accidental ventricular fibrillation was induced mechanically by the application of the epicardial electrode to the boundary of the infarct were discarded from the results.

Expression of data. Calculations of group differences, paired data analysis, and their statistical significance were performed by standard statistical methods.[27] Results are expressed as means ± SEM (number of observations).

Results and discussion

Of the 38 baboons with acute myocardial infarction 25 (66 per cent) spontaneously developed ventricular fibrillation (V.F.). On all occasions V.F. did not spontaneously revert and was not artificially interrupted. All 10 control baboons survived 1 hour of observation. The results are analyzed in relation to the incidence of V.F. or survival for the first hour after coronary artery ligation or in the case of sham operations for a control period of one hour.

I. AGE AND SEX OF ANIMALS AND SIZE AND SITE OF INFARCTION. *Age* was related

Table V Relation between ventricular bigeminy (V B) and incidence of ventricular fibrillation (V F)

	Group with V F†	*Group with 1 hr survival*	*p value*
Number of baboons	17	6	
Total number of episodes of V B	36	10	
Incidence	36/17 = 2 11	10/6 = 1 66	
Coupling interval per animal			
Variable	5	0	
Constant	12	6	
First time of appearance of V B before end in min			
Mean ± SEM	16 ± 2	34 ± 5	p < 0 001
Number	17	6	
Last time of appearance of V B before end in min.			
Mean ± SEM	5 ± 2	19 ± 6	p < 0 001
Number	17	6	

*V B = ventricular bigeminy
†V F = ventricular fibrillation

fibrillation (Table IV) but this is probably due to age since we found no spontaneously hypertrophied or dilated hearts in our series of healthy baboons It is known that a certain critical mass of myocardium is necessary to maintain the fibrillation activity in the ventricle[22,24]

2 HEART RATE Before thoracotomy the initial heart rate was 95 ± 4 beats per minute for the over all group which corresponds well with the telemetrically measured rate of 82 beats per minute in 4 awake adult baboons who were at rest[25] The heart rate after thoracotomy and before coronary artery ligation was 102 ± 4 beats per minute The increase of heart rate was due to the surgical procedure with further increases of heart rate due to intravenous injections of pentobarbital given to maintain anesthesia The final heart rate of 121 ± 4 beats per minute in surviving baboons corresponded to the rate in mildly exercised baboons[25] There was no difference between the heart rate of the baboons of the control group (no arterial ligation) and the baboons who developed ventricular fibrillation or survived the first hour and V F occurred at any heart rate between 60 and 200 sinus beats per minute

3 BRADYARRHYTHMIAS The rarity of bradyarrhythmias and the absence of asystole corresponded with the findings of other investigators[36,37] and is probably explained by the fact that we never ligated the right coronary artery and its branches to the sinus node and the atrioventricular node Nor did we ligate the initial part of the anterior descending coronary artery with its multiple perforating ventricular septal branches nor the proximal third of the circumflex coronary artery with its left atrial branch Bradyarrhythmia did not precede primary ventricular fibrillation which is in agreement with the findings of some authors[15,39] and in contradiction to the findings of others[4,22,40,41]

4 ARRHYTHMIAS WARNING OF VENTRICULAR FIBRILLATION Ventricular bigeminy ventricular tachycardia and R-on T beats were the three most common arrhythmias preceding ventricular fibrillation and frequently appeared on several occasions in the same animal The duration of the attack of ventricular bigeminy was the longest in the group which developed V F (Table V)

The incidence or the number of ventricular bigeminy attacks per animal was not helpful in distinguishing survival from V F There was however a significant difference between the appearance time of the attack of ventricular bigeminy comparing the group who survived and the group who developed V F ($p < 0.001$) Ventricular bigeminy with a variable coupling interval was always followed by V F Ventricular

Table III *Correlation between number of ligations size of infarct, and incidence of surviv*

Number of ligations	Group with V F*		Group with survival for 1 hour		% surviving for 1 hour
	Number	Infarct size (Mean ± SEM)	Number	Infarct size (Mean ± SEM)	
0	0	—	10	—	100
1	19	12 ± 1%	12	8 ± 1%	44
2	6	11 ± 2%	1	11%	14

*Abbreviations VF = ventricular fibrillation

Table IV *Relation between size of infarct total wet weight of heart and mortality rate*

	Control group	Infarct group with survival for 1 hour	Infarct group with V F*
Total wet weight of heart in grams (Mean ± SEM) Number	114 ± 14 (10)	99 ±10 (13)	123 ±7 (25)
P value	$p > 0.05$ (control vs. survival)	$p < 0.05$ (survival vs. VF)	
Size of infarct as % of total heart weight	—	8 3 ± 0 9 (13)	11 9 ±1 1 (25)
		$p < 0.01$ (survival vs. VF)	

*VF = ventricular fibrillation

survived larger infarcts than males Other authors[30] found a good correlation between the size of the infarct and the incidence of V F in dogs and pigs

In the group with *anterolateral* infarct all 7 baboons developed V F The average size of the infarct was significantly larger than the over all size of the infarct of all baboons with V F ($p < 0.025$) (Table II)

The average size of the infarct in the group with *inferior* infarct was identical in the groups who survived or developed V F thus parameters other than size and site of infarct must have operated The group of baboons with a *posterior* infarct and V F had the same size of infarct (nearly 10 per cent) as most other groups but developed V F later than all other groups with infarct and V F ($p < 0.05$)

In the group with *inferoposterior* infarct 3 of 4 of the baboons developed V F We believe that anterolaterally situated infarcts result in large sized infarcts with increasing risk of developing V F[31] The largest sized infarcts with survival were found in the anteroseptal apical area These findings contrast with the findings in the greyhound dogs in whom *anterolateral* infarcts were relatively free from the development of ventricular fibrillation whereas fibrillation occurred more readily in *anteroseptal* infarctions[32]

The average *time of onset* of V F was 30 to 35 minutes after the ligation of the coronary artery Infarcts due to *double occlusion* of two coronary artery branches with contiguous blood supply had only a 14 per cent survival rate for an average sized infarct (Tables II and III)

The total wet *heart weight* was directly proportional to the incidence of ventricular

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Incidence	36/17 = 2 11	10/6 = 1 66	
Coupling interval per animal			
Variable	5	0	
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First time of appearance of V B before end in min			
Mean ± SEM	16 ± 2	34 ± 5	p < 0 001
Number	17	6	
Last time of appearance of V B before end in min			
Mean ± SEM	5 ± 2	29 ± 6	p < 0 001
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Table III Correlation between number of ligations, size of infarct, and incidence of survival

Number of ligations	Group with V F* Number	Group with V F* Infarct size (Mean ± SEM)	Group with survival for 1 hour Number	Group with survival for 1 hour Infarct size (Mean ± SEM)	% surviving for 1 hour
0	0	—	10	—	100
1	19	12 ± 1%	12	8 ± 1%	44
2	6	11 ± 2%	1	11%	14

*Abbreviations VF = ventricular fibrillation

Table IV Relation between size of infarct, total wet weight of heart, and mortality rate

	Control group	Infarct group with survival for 1 hour	Infarct group with V F*
Total wet weight of heart in grams (Mean ± SEM)	114 ± 14	99 ± 10	123 ± 7
Number	(10)	(13)	(25)
P value	$p > 0.05$ (control vs. survival)	$p < 0.05$ (survival vs. V F)	
Size of infarct as % of total heart weight	—	8.3 ± 0.9 (13)	11.9 ± 1.1 (25)
		$p < 0.01$	

*VF = ventricular fibrillation

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The average *time of onset* of V F was 30 to 35 minutes after the ligation of the coronary artery. Infarcts due to *double occlusion* of two coronary artery branches with contiguous blood supply had only a 14 per cent survival rate for an average sized infarct (Tables II and III).

The total wet *heart weight* was directly proportional to the incidence of ventricular

Table VIII Correlation of warning arrhythmias with incidence of ventricular fibrillation and survival rate

	Group with V F		Group with 1 hr survival	
Warning arrhythmia	24	a	b	6
No warning arrhythmia	1	c	d	17

$$\frac{\{[(d - b) - 1/2]^2\}}{(+b)(b+d)(+)(+d)} = 22\ 2 \qquad p < 0\ 001 \quad (= 48)$$

Coeffic t of ssoc tion $\frac{d - b}{d + b} = 0\ 975$

Coeffic nt f rrel t n $\frac{d - b}{\sqrt{(+b)(b+d)(+)(+d)}} = 0\ 723$

Table IX Frequency of ventricular fibrillation following each warning arrhythmia

Warning arrhythmia	*Number of baboons with V F**	*Number baboons with survival for 1 hour*	*% developing V F*
R on T	9	4	69
Ventricular bigeminy	17	6	74
Ventricular tachycard a	11	1	91
More than 5 premature ventricular ectopic beats/min	7	2	77

*V F = t lar fib ll ti

Table X Relation between number of warning arrhythmias and incidence of ventricular fibrillation

Number of arrhythmias	*Total number of baboons*	*Number with V F†*	*% V F*
0	18	1	5
1	17	15	88
2	8	5	63
3	5	4	80

*V t lar b g m y nt cular tachycard or R T ph omen n.
†V F = tri lar fib ill tion.

An approximate quantitative assessment of the ventricular irritability is derived from the average time interval between the first time of the appearance of each arrhythmia and the time of the onset of ventricular fibrillation This time interval is the prediction time for imminent ventricular fibrillation for each arrhythmia and is obtained when the average time interval between the first appearance of each arrhythmia and the time of onset of V F is taken and twice the standard time error is added The practical value of this observation is that ventricular tachycardia ventricular bigeminy and R on T beats in the presence of acute myocardial infarction lose their value in predicting imminent V F once more than 30 20 or 10 minutes (respectively) have elapsed after the arrhythmia has commenced

Table VI Relation between ventricular tachycardia (V T) and incidence of ventricular fibrillation (V F)

	Group with V F *	Group with 1 hr survival
Number of baboons	11	1
Total number of episodes of V T †	47	3
Duration of episodes of V T in sec	5	1 5
(Mean ± SEM)	± 2	± 0 3
First time of appearance of V T		
before end in min	21	50
(Mean ± SEM)	± 5	
Number	(11)	(1)
Last time of appearance of V T		
before end in min	6	50
(Mean ± SEM)	± 2	
Number	(11)	(1)

*V F = ventricular fibrillation
†V T = ventricular tachycardia

Table VII Relation between R on T phenomenon and incidence of ventricular fibrillation (V F)

	Group with V F *	Group with 1 hr survival	P value
Number of baboons	9	4	
Total number of R on T beats	15	4	
First time of appearance of			
R on T before end in min	4 5	36	
(Mean ± SEM)	± 3	± 7	$p < 0\ 0025$
Number	(9)	(4)	
Last time of appearance of R on T			
before end	67 sec	36 min	
(Mean ± SEM)	±15	± 7	$p < 0\ 0025$
Number	(9)	(4)	

*V F = ventricular fibrillation

tachycardia was highly specific in predicting V F (Table VI)

The development of R on T beats could be followed by V F within 1 to 5 min thereafter V F did not occur frequently ($p < 0\ 0025$, Table VII) The presence of one or more of these 3 warning arrhythmias or the absence of all 3, correctly predicted imminent V F or survival for 1 hour in 41 of 48 baboons (85 per cent) after myocardial infarction or sham operation (Table VIII) It was possible to predict V F in 24 of the 25 who developed V F —i e the accuracy was 96 per cent Survival after 1 hour was correctly predicted in 17 of 23 baboons (74 per cent accuracy) The incidence of the 3 warning arrhythmias thus somewhat overestimated the risk of imminent V F All 10 control baboons survived one of these developed ventricular bigeminy which lasted for 2 seconds

Each warning arrhythmia itself had about a 75 per cent incidence of V F and the appearance of more than one arrhythmia per animal did not increase the risk of developing V F (Tables IX and X) The appearance of these 3 arrhythmias in the presence of acute myocardial infarction indicates electrical disturbances of the ischemic ventricle and all have a similar qualitative value in estimating developing electrical instability

in predicting the time that ventricular fibrillation subsequently develops

Summary

Factors associated with the development of ventricular fibrillation after coronary artery ligation were studied in a subhuman primate (Cape Chacma baboon). In 25 or 66 per cent of 38 baboons primary ventricular fibrillation occurred within the first hour after the onset of acute myocardial infarction. Increasing age, total heart weight, and the size of the infarct were directly related to the incidence of primary ventricular fibrillation. Anterolateral infarcts had the highest risk of ventricular fibrillation. Anteroseptal and posterior infarcts had the best survival rate for the first hour. Male baboons were more prone to develop ventricular fibrillation than were females. There was no definite progression from ventricular ectopic beats to ventricular fibrillation. In the presence of ventricular tachycardia (even when brief in duration), ventricular bigeminy, or R on T beats, ventricular fibrillation has to be expected from the time of onset of the arrhythmia till 30, 20, or 10 minutes have elapsed, respectively. Beyond these times ventricular fibrillation did not develop during the experimental period. Conversely, the absence of these signs could predict survival for 1 hour. The over-all efficiency of the warning signs in predicting ventricular fibrillation or survival was 85 per cent. Ventricular fibrillation occurred without any of these 3 warning signs in only 1 baboon (5 per cent of all cases). It is suggested that these warning arrhythmias could have a practical value in the management of patients with acute myocardial infarction of recent onset by anticipating the time of impending ventricular fibrillation.

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A frequency of more than 5 isolated premature ventricular ectopic beats per minute, appearing after the descent of the T wave, is a well known sign indicating electrical instability after acute myocardial infarction However in our series this sign was less frequent than ventricular bigeminy and tachycardia or the R on T phenomenon (Table IX) When it occurred it was always associated with at least one of the 3 previously mentioned arrhythmias and adding the frequency of ectopic beats did not alter the efficiency of prediction of imminent VF Bennett and Pentecost,[42] in a recent study in patients in a Coronary Care Unit, and Moss and associates[29] did not find the frequency of single ventricular ectopic beats to be a good warning sign Furthermore single ventricular ectopic beats may only have a warning value if they originate in the left ventricle [14,42] In practice it is difficult to site ventricular origin of an isolated ectopic beat with the single classic precordial bipolar monitor lead used in coronary care units generally two simultaneously recorded standard leads are necessary to place the origin of the ventricular ectopic focus One minute of continuous electrocardiographic recording or counting is often necessary to detect the arrhythmia This procedure is more time consuming than detecting the other 3 warning arrhythmias selected here

Other arrhythmias such as sinus tachycardia ventricular trigeminy, and ballet rhythm[44] were infrequently present No constant pattern of rhythmicity of ventricular arrhythmias or progressive increase of the quantity of ventricular ectopics preceding ventricular fibrillation could be detected

Conclusion

Previous authors have found that the period of susceptibility to early ventricular fibrillation in dogs with acute coronary artery occlusion was short in duration and that fibrillation was initiated by a paroxysm of ventricular ectopic beats accelerating in frequency [45,48] These authors drew attention to the causal relationship between progressive increase of ventricular premature beats and the initiation of ventricular fibrillation However, this pattern of events was not usual in our study of the baboon, and is also infrequent in patients with acute myocardial infarction [14,42] Thus a search had to be made for other warning signs of ventricular fibrillation

Hill and colleagues[26] found 57 episodes of primary ventricular fibrillation in 18 of 26 rhesus monkeys within the first 40 minutes of the onset of acute myocardial infarction Each time ventricular fibrillation was electrically stopped Apart from premature ventricular ectopic beats immediately after the coronary artery occlusion, they found no other complex ventricular arrhythmias preceding VF We believe that this apparent lack of warning signs is due to the marked increased of sinus rhythm (200 to 240 beats per minute) of the conscious animals suppressing any slower ventricular focus and to the fact that no continuous ECG rhythm recording was undertaken during the first hours after the acute myocardial infarction Blood biochemical changes found after infarction have not yet been proved to have a practical value in predicting imminent ventricular fibrillation in patients with acute myocardial infarction [10,39]

Although an open chest procedure with general anesthesia and artificial respiration must to some extent interfere with the natural course of acute myocardial infarction these conditions allowed free choice of the site of the infarct accurate assessment of the infarct size by use of epicardial ECG mapping and of the time of the onset of the infarct Ideally non anesthetized closed chest baboons should be studied but the awake baboon can be vicious and is not readily studied in a laboratory

If these 3 warning arrhythmias of imminent ventricular fibrillation in the baboon are applicable to patients with acute myocardial infarction the practical implications would be most important The warning signs could detect developing ventricular electrical instability and time the onset of primary ventricular fibrillation of patients in coronary care units especially those admitted shortly after the onset of their symptoms

To our knowledge this is the first report showing the value of warning arrhythmias

Cardiovascular events in anxiety
Experimental studies in the conscious dog

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During recent years attention has been increasingly focused on the possibility of controlling the emotional aspect of angina pectoris. Several minor tranquilizers—i.e., benzodiazepine derivatives—have been synthetized and some of these have proved to be of help in the management of the anxious anginal patient, especially when combined with long acting nitrates.[1,2] Beta receptor blocking agents have also been used[3-5]; the usefulness of these compounds in emotional state has been based on the assumption that the autonomically mediated somatic symptoms—especially those referable to cardiovascular events—may themselves reinforce anxiety when there exists a conscious association between these symptoms and anginal pain. If so, blockade of beta adrenoceptors would interrupt the somatopsychic sequence of events which are likely to be involved in the maintenance of anxiety in anginal patients.

Despite the interest in clinical cardiology, little research has been reported on the cardiovascular adjustments occurring in anxiety, and consequently the influence of tranquilizers and beta blockers on the hemodynamic changes brought on by this emotional state has not been defined. The majority of the reports have dealt with changes in heart rate.[6-9] Arterial pressure[10,11] and flow measurements[12] have seldom been used in emotional states in man because of technical difficulties associated with the measurements. Stebbins and Smith[13,14] described conditioned increases in heart rate and peripheral blood flow in monkeys with ultrasonic flow probes implanted on the terminal aorta. No further studies appear to have been reported on directly measured coronary and systemic hemodynamics in emotional states.

The present paper reports the preliminary results of a study designed to investigate the influence of an anxious state induced by a classical conditioning procedure on coronary and systemic hemodynamics in trained conscious dogs; the effect of beta blockade and a minor tranquilizer (temazepam) on the altered hemodynamics was also studied.

Methods

Mongrel dogs with an average weight of 15 kilograms were used in these experiments. In general anesthesia was introduced by intravenous injection of thiopenton 30 mg. per kilogram of body weight and under artificial respiration with oxygen to which halothane (2 per cent to 3 per cent) was added when required, the chest was opened through the fourth left intercostal space and the heart was exposed. The circumflex branch of the left coronary artery was dissected near its origin and an electromagnetic flow transducer was im

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to 2 100 ml per minute Blood flow through the left circumflex coronary artery ranged from 37 to 56 ml per minute with an average stroke flow of 0 58 ml the coronary flow per unit of cardiac work was 20 ml/kg M/min Mean and late diastolic coronary resistance averaged 1 9 and 1 8 mm Hg/ml/min respectively All values were fairly stable throughout the experiments

Responses to S_1 and S_2 The results obtained in the present experiments and the statistical evaluation of the data are reported in Table I Presentation of S_1 during the first experiments did not alter the cardiovascular dynamics of the trained conscious dogs to a relevant extent

Delivery of S_2 at the fiftieth second was followed by cardiovascular changes closely resembling those described previously by Bergamaschi and co workers[19] and by Rayford and colleagues[20] heart rate and cardiac output increased 108 and 120 per cent on control values as aortic pressure increased simultaneously the averaged external work of the left ventricle rose from 2 34 kg M per minute to 4 93 kg M per minute Mean coronary flow increased from 47 to 119 ml per minute and mean and late diastolic resistance decreased 33 and 40 per cent respectively The changes in all cardiovascular parameters in the three dogs except aortic pressure were significant

The coronary and systemic hemodynamic changes brought on by subsequent repetitions of the tone shock combination are shown in Fig 1 Immediately after the continuous tone (S_1) was started heart rate cardiac output left ventricular work and mean coronary flow increased significantly systemic and coronary resistances showed a significant decrease Mean aortic pressure also increased to 137 mm Hg simultaneously with the maximum increase in arterial pressure heart rate slowed down from 202 to 126 beats per minute Peak changes in cardiovascular dynamics were accomplished within 15 to 30 seconds Thereafter all the cardiovascular parameters of the individual dogs decreased remaining however at levels significantly different from normals (Fig 1 and Table I) heart rate was 155 beats per minute and cardiac output averaged 3 598 ml per minute vascular resistance was 38 per cent lower than control The averaged external work of the left ventricle was 4 9 kg M per minute and the left circumflex coronary flow was 95 ml per minute as both parameters were doubled during presentation of S_1 the mean coronary flow per unit work was unchanged Mean and late diastolic coronary resistance decreased 43 and 53 per cent respectively (Table I)

The values of each parameter remained significantly different from controls as long as the tone was left on

When S_2 was not presented interruption of the tone was followed by a rapid return to control values in all cardiovascular parameters (Fig 1)

Effect of beta blockade Propranolol 1 mg per kilogram of body weight was given intravenously at the second minute of presentation of S_1 when the pattern of cardiovascular changes induced by S_1 was fairly steady Three minutes after administration of the beta blocker the increase in heart rate cardiac output left ventricular work and mean coronary flow were markedly depressed while stroke coronary flow increased (Fig 2)

The activity of propranolol was also investigated in a second group of trained conscious dogs in which heart rate was challenged with the infusion of increasing doses of isoprenaline In these experiments propranolol antagonized 78 per cent the cardiac acceleration provoked by the exogenous stimulation of β adrenoceptors (see Table II and Fig 4)

Effect of the tranquilizer Temazepam (methyl oxazepam) 10 mg per kilogram of body weight was given orally one hour before presentation of S_1 The dose and the time were selected according to the results previously obtained in rats by Longoni Mandelli and Pessotti[21] and by Longoni and colleagues[22] The effect of the tranquilizer on systemic and coronary hemodynamic changes provoked by S_1 are shown in Table I and a typical tracing is given in Fig 3 The increase in heart rate cardiac output and left ventricular work were depressed to levels not significantly different from controls

Although peripheral and coronary vascular resistances increased after temazepam 10 mg per kilogram of body weight they remained significantly lower than in the quiet state Stroke coronary flow was higher

planted on the artery, a pneumatic cuff was applied distal to the coronary flow-probe and inflation of this cuff to occlude the artery was used to determine zero flow postoperatively. A larger flowprobe was applied around the ascending aorta and an indwelling catheter was implanted in the aortic arch; the connecting wires and the catheter were brought out to the back. Experiments were not started until the dogs had completely recovered from surgery.

Aortic and coronary flow tracings were obtained by means of an electromagnetic flowmeter (Biotronex Laboratories); phasic and mean aortic pressure were measured by a Statham P23Db transducer connected to the aortic catheter; the electrocardiogram was obtained by parasternal electrodes. All signals were recorded on an 8 channel Beckman Type R Dynograph. Stroke aortic volume and stroke coronary flow were measured by planimetry of the areas beneath the phasic flow patterns.

The following parameters were calculated: mean vascular resistance: mean aortic pressure/mean flow; late diastolic (L.D.) coronary resistance: L.D. aortic pressure/L.D. coronary flow; vascular resistances were expressed as mm. Hg/ml./min. Left ventricular work/time was calculated as a product of cardiac output (liters per minute) and mean aortic pressure (mm. Hg × 13.6) and expressed in Kg.m./min.

Conditioning procedure. The experiments were carried out in daylight in a laboratory with the dogs lying on either side on a padded platform. Following the experimental model described by Estes and Skinner[15] anxiety was induced in the dogs by repetitive presentations of two subsequent stimuli: S_1, the conditioning stimulus and S_2, the unconditioned stimulus. The former is an initially neutral stimulus which prior to training does not affect the animal's behavior to any relevant extent; the latter is a noxious stimulus which establishes the aversive drive.[16] In our experiments S_1 was a continuous, low frequency tone, and S_2 was a shot from a starting pistol.

During training the tone was left on for 50 seconds; at that time the shot was delivered and the tone was stopped. $S_1 \rightarrow S_2$ combination was presented to each dog once a day. On subsequent repetition the temporal relationship $S_1 \rightarrow S_2$ was progressively lengthened until S_1 alone was able to maintain the conditioned emotional responses in the recorded cardiovascular parameters.

The mean values for each parameter obtained in control state in anxiety and after treatment with temazepam were compared by analysis of variance. This was carried out following a two way cross classification: treatments and dogs.

Antagonistic activity to stimulation of β adrenoceptors. The effect of propranolol and temazepam on the cardiac acceleration provoked by isoprenaline was studied in a second group of four conscious trained dogs. Two series of increasing doses of isoprenaline were infused intravenously with a two hour interval between them. Each animal received propranolol and temazepam on separate days: propranolol 100 μg per kilogram of body weight was injected intravenously 15 minutes before the second isoprenaline infusion and temazepam was administered orally 1 hour before the second series of infusions.

Log dose response curves to isoprenaline before and after the two drugs were calculated by the least squares method and the distance between the two curves (M) was estimated on the abscissae. M values for propranolol and temazepam were submitted to a two way analysis of variance: treatments and dogs. The potency ratios (P.R.) of isoprenaline were calculated as antilog of M values for propranolol and temazepam.

Results

Control data. Before the conditioning was started each dog was trained to lie quietly on either side on the padded platform while observations were being made. To avoid stress to the animals the same people handled the dogs throughout. Once trained all the dogs gave hemodynamic values similar to those previously reported by Gregg and co-workers[17] and by Bergamaschi and colleagues.[18] Individual dogs had different heart rates which were in the range of 68 to 93 beats per minute. The average value of mean aortic pressure was 88 mm. Hg and cardiac output ranged from 1,800

Table I Averaged results from 3 conscious dogs obtained in resting quiet state (Normal) during presentation of the conditioning stimulus S_1 before (Anxious), and 1 hour after oral administration of tema epam 10 mg per kilogram of body weight (Anxious + tema epam)

Experiment	No dogs	Heart rate bts/min	Aortic blood pressure mm Hg	Cardiac output ml./min	Total peripheral resistance mm. Hg/ml./min	Left vent. work kg-m./min	Coronary flow: Mean ml./min.	Coronary flow: Stroke ml.	Coronary resistance: Mean mm. Hg/ml./min.	Coronary resistance: Late diast. mm. Hg/ml./min.
Normal (N)	3	82 ± 7 23	88 ±3 05	1980 ± 63 40	0.045 ±0 003	2 34 ±0 04	47.5 ± 5.81	0.58 ±0 07	1.90 ±0 19	1.50 ±0.29
Anxious (A)	3	155 ±13.66	101 ±1 08	598 ±133 14	0 0.8 ±0.007	4 93 ±0.57	95 ±15.89	0 60 ±0.09	1 08 ±0.07	0 85 ±0 09
Anxious + temazepam (T)	3	90 ± 2 49	89 ±2 94	2314 ±114.50	0.039 ±0 003	.79 ±0 07	0 ± 3 1	0.77 ±0 05	1 77 ±0 03	1 07 ±0 07
N → A	P	<0 01	>0 05	<0 01	<0 01	<0 01	<0 01	>0 05	<0 01	<0 01
A → T	P	<0 01	>0 05	<0 01	<0 01	<0 05	>0 05	>0 05	>0.05	>0 05
T → N	P	>0 05	>0 05	>0 05	<0.05	>0 05	>0 05	<0 05	<0 01	<0 05

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than that recorded at the same time in control experiments and the *coronary flow* per unit work was significantly increased from 19 ± 1 70 to 25 ± 1 77 ml per kilo gram per minute ($P < 0.05$)

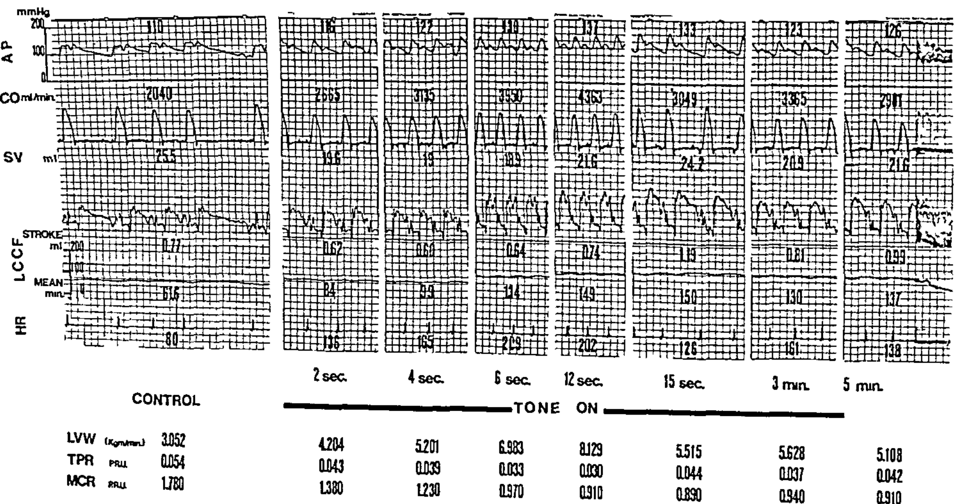
Temazepam 10 mg per kilogram of body weight administered by oral route 1 hour before isoprenaline did not alter the heart rate changes induced by the intravenous infusion of isoprenaline (see Table II and Fig 4)

Discussion

In the classical conditioning procedure anxiety is the anticipatory response to an *unpleasant event set* up by presentation of an initially neutral stimulus (S_1) which was followed in the past by the aversive stim ulus (S_2) [15]

The changes in heart rate arterial pres sure and peripheral flow that occur in this emotional state which *somewhat resem* bles fear are associated with activation of the autonomic nervous system and cen trally evoked somatic *motor activity—i e* uncontrolled respiration tremor and move *ments of the* head These observations lead us to suggest that the anticipatory changes in the cardiovascular system are likely to be determined *both* by *the* increased sym pathetic drive to the heart and vasculature and the increased oxygen demand from the muscles [5] In order to avoid the possible influence of the increased muscular metabo *lism on cardiac and vascular dynamics* the dogs used in the present experiments were trained to lie still avoiding gross muscular *movements during aversive* stimulation we therefore omitted any operative re sponse Consequent to training basal levels *of the recorded* cardiovascular parameters in the dogs were satisfactorily low this agrees with the results obtained in previous *studies in man* [3] *and in resting* conscious dogs [18 24] which showed that sympathetic activity to the heart and vessels is minimal *in the resting state in the supine* position

Delivery of the aversive stimulus (S_2) was followed by marked cardiovascular changes *heart rate cardiac output left* ventricular work and blood flow through the left circumflex coronary artery increased significantly *peripheral and coronary re* sistances were markedly depressed the changes in aortic pressure were not sig nificant The cardiovascular *response to the* aversive stimulus (S_2) was relatively con *stant on separate days and was always* accompanied by *increased respiratory* ac tivity and by movement of the head The hemodynamic changes brought on by S_2 in the present *experiments are* similar to those evoked by stress in the conscious *dog* [19] which are mediated through activa tion of the sympathetic nervous system as they were largely depressed by blockade of



		CONTROL	2 sec.	4 sec.	6 sec.	12 sec.	15 sec.	3 min.	5 min.
LVW	(Kgm/min)	3.052	4.204	5.201	6.983	8.129	5.515	5.628	5.108
TPR	PRU	0.054	0.043	0.039	0.033	0.030	0.044	0.037	0.042
MCR	PRU	1.780	1.380	1.230	0.970	0.910	0.890	0.940	0.910

1 Sections from a continuous record in a trained conscious dog lying on its right side showing the changes in systemic and coronary hemodynamics brought by presentation of a conditioning stimulus (*tone*). At the 5th minute the tone is stopped. AP = aortic pressure. CO = cardiac output. SV = stroke volume. CF = phasic (stroke) and mean (*mean*) blood flow through the left circumflex coronary artery. HR = heart rate and electrocardiogram.

Table II. Analysis of variance of the M values (see text) for propranolol and temazepam and potency ratios (P.R.) of isoprenaline before and after administration of the two drugs

Source of variation	*d.f.*	*Mean square*	*F*	*P*
Treatments (propranolol → temazepam)	1	0.9503	19.15	<0.05
Dogs	3	0.0256	<1	>0.05
Residual	3	0.0496	—	—

$$P.R. \frac{\text{isoprenaline} + \text{propranolol}}{\text{isoprenaline alone}} = 0.217$$

(fiducial limits for P = 0.05: 0.086–0.549)

$$P.R. \frac{\text{isoprenaline} + \text{temazepam}}{\text{isoprenaline alone}} = 1.063$$

(fiducial limits for P = 0.05: 0.7202–1.569)

edly depressed the anticipatory changes in the cardiovascular system: the increases in heart rate, cardiac output, left ventricular work, and coronary flow were reduced. The effect on coronary flow was rate dependent as stroke coronary flow increased after propranolol. The results obtained with propranolol in the present experiments are further evidence that the conditioned changes in the cardiovascular system are largely mediated by activation of the sympathetic nervous system and adrenergic beta adrenoceptors in the heart and vessels initiated by activation of the regulatory structures in the limbic system.[18, 31] We cannot answer the question whether the efficacy of propranolol in blocking the somatic symptoms of anxiety is due to a direct action on the central nervous system or to a peripheral action on the beta adrenoceptors in the cardiovascular system. An attempt to solve the question was made by Bonn, Turner, and Hicks,[5] who reported that autonomically mediated somatic symptoms of anxiety in anginal patients were improved after practolol 200 mg twice daily. As very little practolol enters the central nervous system, it seems unlikely that its efficacy is related to a direct central action; a peripheral beta adrenoceptor blocking action is more probable.

Oral administration of temazepam, a benzodiazepine derivative, prevented the onset of anticipatory reactions in the cardiovascular system evoked by anxiety: the increases in heart rate, cardiac output, and left ventricular work were largely depressed by the drug; somatic reactions also appeared diminished.

The observation that anticipatory reactions had returned to pretreatment levels on the following day indicates that the results obtained after temazepam were not influenced by a possible extinction of the emotional conditioned response consequent to removal of the unconditioned stimulus (S_2).

The neurophysiological mechanism by which temazepam depresses the altered cardiac and systemic hemodynamics in anxiety is likely to be similar to that obtained by Guerrero-Figueroa and colleagues[20, 21] in conscious cats and monkeys using other benzodiazepine derivatives. They suggested that certain benzodiazepine derivatives depress the levels of anxiety, tension, and fear, possibly as the result of their ability both to activate the nervous structures involved in the rewarding system and to inhibit the structures responsible for aversive behavior.

The possibility that the effect of temazepam is mediated through a peripheral action on the sympathetic adrenergic receptors can be excluded, since in the present experiments the tranquilizer did not alter the heart rate response to isoprenaline.

Although the increase in left circumflex coronary flow per minute produced by anxiety was depressed by the previous oral

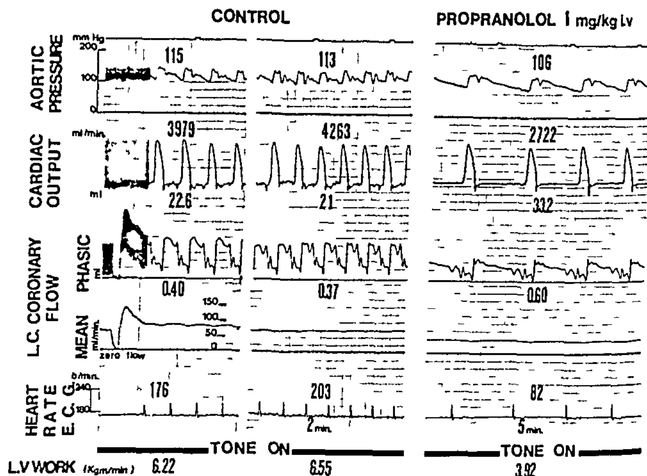


Fig 2 Effect of propranolol on anticipatory responses in the coronary and systemic hemodynamics in a dog lying on its right side Propranolol 1 mg per kilogram of body weight was given intravenously at the second minute of the presentation of the conditioning stimulus

the sympathetic beta adrenoceptors [19]

The anticipatory reactions in the cardiovascular system evoked by the conditioning stimulus (S_1) after training were qualitatively similar to those brought on by S_2 They started *a few seconds after the onset* of the tone (S_1) and reached their maximum from the fifteenth to the twentieth seconds Reflex slowing of heart rate was commonly observed simultaneously with the peak increase in arterial pressure During bradycardia stroke and mean coronary flow further increased while coronary resistance decreased, this was caused by the concurrent presence of a relatively high aortic pressure, an increased duration of the diastole, and a *decrease in the extravascular* myocardial factors acting on the coronary vessels All the recorded cardiovascular parameters stayed *thereafter slightly* below the peak effect levels remaining however, significantly different from normal values, increased respiratory activity was always present Similar results were obtained by Smith and Stebbins[14] in conscious monkeys they reported conditioned increases in peripheral blood flow and heart rate and contended that these were true *conditioned responses not secondary* either to respiratory or skeletal muscle activity The autonomic mediation of the somatic symptoms of anxiety has been demonstrated by the observation that the emotional state is associated with increased catecholamine release[25] and F F A mobilization [26] In clinical research in anginal patients Turner and colleagues[3,4] showed that autonomically mediated somatic symptoms of anxiety were largely abolished by blockade of beta adrenoceptors with D L propranolol while D propranolol, which lacks beta blocking properties was ineffective [27]

In the present experiments blockade of adrenergic beta receptors with propranolol 1 *mg per kilogram of body weight* mark

Case reports

Cerebrovascular accident with unusual electrocardiographic changes

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Recent reports[1-4] and reviews[5-7] have drawn attention to the electrocardiographic (ECG) changes in cerebrovascular disease. The purpose of this case report is to describe interesting and relatively unusual electrocardiographic changes in a ten year old girl with pathologically proven intracerebral hemorrhage.

Case report

The patient, a ten year old girl, was admitted on June 19, 1971, because of a left hemiparesis. The child had previously been in excellent health until the morning of admission, when upon rising she complained of abdominal pain, pain over her right eye, and shortly thereafter developed left hemiparesis. No seizure activity was noted, nor was a history of trauma elicited.

Physical examination revealed a well-developed, poorly responsive female child. The apical heart rate was 60 and irregular, and the blood pressure was 110/ 0 mm. Hg. Respirations were 20 per minute. Cardiac auscultation was unremarkable except for the irregular rhythm. Neurological examination revealed anisocoria, R > L, and both pupils showed a sluggish light response. Dysconjugate gaze was noted. Ophthalmoscopic examination was unremarkable. Left hemiplegia was apparent and was associated with a positive Babinski sign on the left.

Complete blood count, serum sodium, chloride, CO_2 content, blood urea nitrogen, calcium, and urinalysis were all normal. Serum potassium was 2.8 mEq./L. Arterial oxygen saturation was 96.6 per cent and Pco_2 was 40.0 mm. Hg. Arterial pH was 7.308. Sickle cell preparation was negative. Chest x-ray and skull films were unremarkable. Cerebral angiograms were within normal limits. Lumbar puncture revealed grossly bloody cerebrospinal fluid.

A rhythm strip obtained in the emergency room (Fig. 1, *top*) demonstrated Mobitz Type I second degree AV block with junctional escape beats and periods of AV dissociation. The patient was given 0.3 mg. of atropine intravenously, and 1:1 conduction resumed with sinus tachycardia and wandering atrial pacemaker (Fig. 1, *bottom*). The child's clinical course deteriorated with deepening coma and hypothermia (rectal temperature 94° F.). A 12 lead ECG at that time (Fig. 2) revealed sinus bradycardia with a rate of 50 per minute and a P-R interval of 0.18 second. The ST segment was elevated. Maximal ST segment elevation occurred in Leads V_2, V_3, and V_4, with an elevation exceeding 5 mm. The QT interval was 0.64 second and QTc was 0.58 second. The patient died 29 hours after admission.

Necropsy examination was unremarkable except for the findings in the central nervous system

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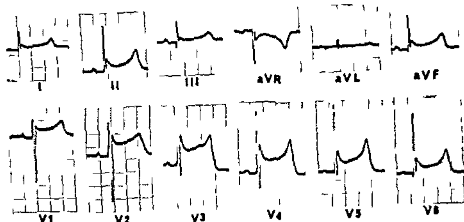


Fig 2 Twelve lead electrocardiogram approximately 24 hours after admission (see text)

that intracerebral disease may induce subendocardial hemorrhage[6] and ultrastructural myocardial changes [2,23] Such changes may be of sufficient magnitude to induce Q waves[6] While the association between cerebrovascular accidents and myocardial infarction has been made in patients prone to both conditions[16] the question may be raised as to whether ST segment elevation may be due to myocytolysis alone The case reported demonstrated normal microscopic examination of the heart suggesting that the ST segment changes were mediated either by alteration of autonomic tone pH electrolyte disturbances or a combination of all of these factors

Summary

This case report describes a 10 year old girl sustaining a cerebrovascular accident secondary to a vascular malformation involving the cingulate gyrus The patient developed a Mobitz Type I block with periods of AV dissociation A 12 lead electrocardiogram revealed the frequently observed prolongation of the QT interval Her ECG also demonstrated diffuse ST segment elevation Neurophysiological mechanisms are discussed

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Fig. 1 *Top panel* Rhythm strip of the patient on admission demonstrating Mobitz Type I AV block with periods of AV dissociation *Bottom panel* Restoration of 1:1 conduction with wandering atrial pacemaker after 0.3 mg atropine intravenously

A vascular malformation was found to involve the cingulate gyrus at the right frontal parietal junction This vascular malformation had ruptured resulting in intraventricular and subarachnoid hemorrhage Transtentorial and transforaminal herniation had occurred

Discussion

The case reported is characterized by two *interesting electrocardiographic changes*

Fig 1 demonstrates second degree AV block and periods of AV dissociation with return of AV conduction to normal following administration of atropine To our knowledge the Wenckebach block seen in this patient clearly related to a cerebrovascular accident has not been previously described although 2:1 block has been observed [4]

Recent papers[8-11] have drawn attention to the fact that increased vagal tone contributes to the development of the observed arrhythmias in cerebrovascular accident Experimental studies[12] have shown that the production of Wolff-Parkinson-White preexcitation and AV dissociation[8,12] may occur with electrical stimulation of the mesencephalic reticular formation or the dorsomedial hypothalamic nucleus These experimental studies suggest that enhanced vagal tone significantly contributes to the development of various cardiac arrhythmias Such enhanced vagal tone may be a result of stimulation of vagal fibers innervating the circle of Willis [13] enhanced vagal tone secondary to the baroreceptor reflex [3] *or stimulation of Area 13 the chief cortical* representation of the vagus nerve [9] In our patient the lesion involved the cingulate gyrus containing Areas 23 24 and 32 These areas are thought to control autonomic functions of the heart [9,14] Thus involvement of the cingulate gyrus may have *accounted for the observed cardiac arrhythmia*

A second interesting feature of this case is the ST and T wave changes Cerebrovascular accidents are as a rule associated with ST segment prolongation and depression[1] and T wave inversion [1,3] occasionally simulating myocardial infarction [1,16] On *the other hand ST segment elevation is less* frequently observed [16] It has been proposed[1] that such changes may be secondary to electrolyte imbalance pH and blood gas abnormalities the latter supported by experimental studies [17,18] Abnormalities of serum K^+ and pH were observed in the *reported case and may have contributed* to the ECG pattern of elevated ST segment [18] Hypokalemia has also been implicated in the development of second degree heart block [19] The second positive deflection at the J junction (Fig 2 Leads II III aVF and V_3 through V_6) as well as the prolonged QT may have been due in part to hypothermia [20,21] in addition to enhanced vagal tone

Experimental studies have [illegible] rated

Malfunction of a Cutter-Smeloff mitral ball valve prosthesis Diagnosis by phonocardiography and echocardiography

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Although ball variance is a relatively frequent complication associated with aortic ball valve prosthetic valves[1,2] similar malfunction of mitral prostheses is uncommon[4-11] This is a case report of malfunction of a Cutter Smeloff mitral ball valve prosthesis that was detected phonocardiographically and echocardiographically seven years after implantation

Case report

The patient is a 30-year old man who had three episodes of acute rheumatic fever as a child and had the onset of congestive heart failure at age 16 Two years later severe mitral and mild aortic regurgitation were demonstrated at cardiac catheterization At age 25 (1967) his mitral valve was replaced with a Cutter Smeloff ball valve prosthesis following which he did well postoperatively In 1967 he was placed on anticoagulant following the sudden onset of a transient right hemiplegia In 1971 he had a right sided seizure which was followed by a persistent right hemiplegia

He was admitted in January 1972 for persistent fever myalgia and malaise the cause of which was never definitely established On admission his blood pressure was 110/70 mm Hg pulse 64 and irregularly irregular respiration 15 per minute and oral temperature 38 8 C The peripheral pulses and the jugular venous pressure were normal and the chest was clear The apex impulse was in the anterior axillary line The opening and closing clicks of the prosthesis sounded normal but the interval between A_2 and the opening (O C) interval varied widely There was a Grade 1/6 early decrescendo blowing diastolic murmur along the left sternal border The electrocardiogram (ECG) demonstrated atrial fibrillation and non specific ST changes The chest x ray showed generalized gross cardiomegaly and pulmonary venous congestion

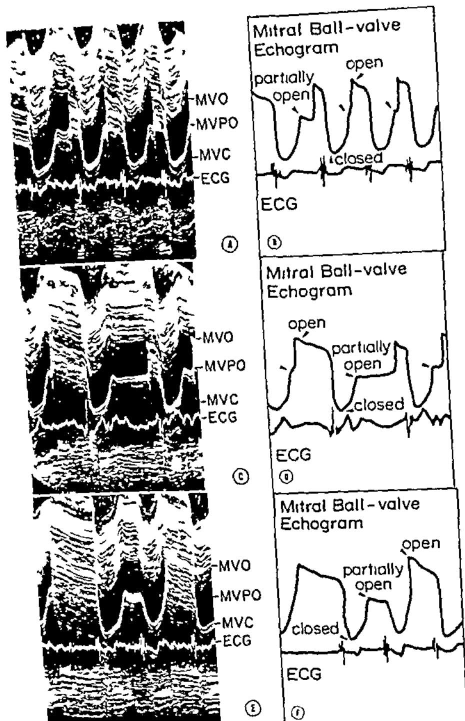
Simultaneous phonocardiography and echocardiography (Fig 1) demonstrated widely varying S_2 opening click intervals the length of which usually varied directly with the R R intervals of the preceding cycles The echocardiogram demonstrated that the transient sticking of the ball (*indicated by a row*) occurred in the partially open position and that the opening click (O C) occurred when the ball was in the maximally open position Additional echocardiograms (Fig 2) showed the same phenomenon as well as one cycle during which the ball did not reach its potential maximal open excursion remaining stuck in the partially open position throughout diastole (Fig 2 *E and F*) Ball valve motion was detected echocardiographically by searching inferiorly and laterally to the position where motion of the anterior mitral left is usually studied

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F g 2 1 through *F* Echocardiograms of mitral ball valve prosthesis MVO = ball in open position MVPO = ball in partially open po tion MVC = ball in closed po it on On the left Polaroid photographs of echocardiograms (A C and E) and on the r ght (B D and F) the corre ponding artist s line drawings of original recording of the malfunction ng Cutte Smeloff mitral valve pro thesis The echocardiograms illustrate the varying degree of valve dysfunction particularly the tendency for the ball to stick in the partially open position d r g part o ll of d a tole with the re ult that the time pent in the partially open posit on frequently var es from b t to beat In the middle beat of *E* and *F* the ball never reaches the fully open po ition It should be oted that nce the echo beam i seldom f ever d rected prec sely along the pathway of the moving ball d ffere t are of the b ll are probably recorded du i g the card ac cycle

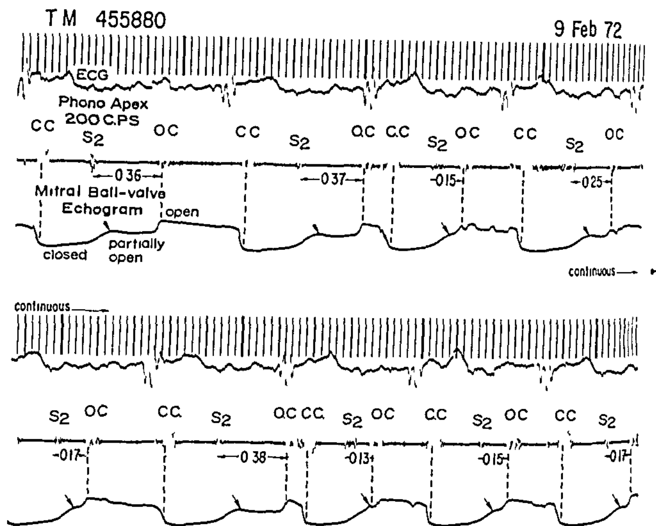


Fig 1 Simultaneous echocardiography and phonocardiography *Phono* = phonocardiogram taken at the apex at 200 cycles per second *C C* = closing click *O C* = opening click S_2 = second heart sound $S_2 - O C$ intervals are shown in seconds (varying from 0 13 to 0 38) The points at which the ball begins to stick in the partially open position are shown by arrows The *O C s* correspond with the arrival of the ball to the fully open position The *C C* corresponds to the ball moving to the closed position The echocardiograms which were recorded in the analog method show a rather consistent location of the maximal anterior movement of the ball coincidental with the opening click This consistency supports the conclusion that the points of the maximal excursion are real rather than artifactual

On February 15 1972 after three weeks of intensive antimicrobial therapy for possible bacterial endocarditis the patient was operated on and the prosthesis was replaced with a Beall disc valve mitral prosthesis The left atrium was markedly enlarged and its posterior wall between the insertion of the left and right pulmonary veins was completely covered with old and recent thrombi which were removed The orifice of the mitral valve was narrowed by the overgrown fibrous tissue over the valvular ring The struts of the valve (Fig 3) were segmentally covered with various size of similar fibrous tissue which impeded the movement of the ball both in the closed position and as the ball passed through the ring of the prosthesis No bacteria were seen microscopically or in cultures obtained at surgery

Comments

Malfunction of a mitral ball valve prosthesis is not commonly recognized but when present is associated with symptoms due to cerebral emboli and/or congestive heart failure [4-11] In several of the cases reported repeated neurological symptoms occurred often months or several years (as in this patient) before the prostheses were eventually replaced Since peripheral embolization and congestive failure frequently occur in patients with rheumatic valvular disease with large left atria and atrial fibrillation their presence does not necessarily implicate a malfunctioning valve as their cause Because of the serious morbidity often associated with systemic emboli and heart failure however the early detection of a malfunctioning prosthetic valve is of obvious importance

Malfunction of a mitral

echocardiographically It would appear reasonable to perform these studies serially at intervals of 3 to 6 months in patients with a mitral ball valve prosthesis and whenever symptoms suggestive of peripheral embolization or of the onset or worsening of congestive heart failure are present

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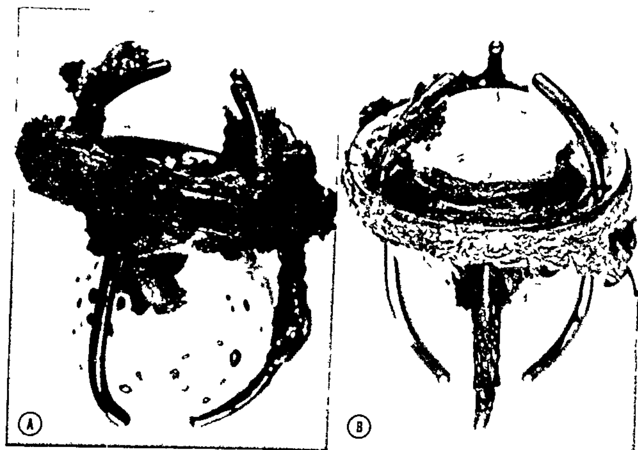


Fig 3 *A* and *B* Photographs of the Cutter Smeloff ball valve prosthesis removed at surgery in the open position (*A*) and in the stuck position as the ball passes through the ring (*B*) There is extensive fibrous overgrowth on the valve ring as well as on the atrial and ventricular struts

thesis can be suspected by prolonged and variable intervals between the second heart sound and the opening click of the prosthetic valve which should normally be less than 0 15 second[5,10,12,13] In all but one of the reports cited above[4,11] the intervals were recorded phonocardiographically and shown to be variable and prolonged Occasionally the opening click was intermittently absent In the one exception[9] the valve sounds were described as being normal but phonocardiography was not performed

In atrial fibrillation the variation of the S_2 opening click intervals with preceding cycle lengths may be explained by the longer diastolic filling phase allowing the left atrium to decompress thereby lowering left atrial pressure and the left atrial to left ventricle pressure difference (This is similar to the changes in the S_2 OS intervals in mitral stenosis[16,18]) The lower pressure gradient causes the S_2 opening click interval to be prolonged and as evidenced in Figs 1 and 2, the interval is also prolonged in malfunctioning prosthesis

Echocardiography appears to be a promising and non invasive technique for the assessment of prosthetic valve function The motion of the prosthetic ball resembles that of the anterior leaflet of the mitral valve in mitral stenosis[13,15] The dimension of the ball as well as its excursion timing and speed of motion are all easily obtained and reproducible at least over short periods of time[14] To our knowledge Pfeifer and associates[11] reported the first use of ultrasound in the detection of prosthetic ball valve malfunction The echograms shown in their report showed that the ball stuck in the closed position whereas in the prosthesis removed from our patient there was a tendency for the ball to be stuck both in the closed posterior position and again as it passed through the ring of the prosthesis

Summary

Mitral ball valve prosthesis malfunction is uncommon but may be associated with serious morbidity and may be fatal The diagnosis may be suspected clinically and confirmed phonocardiographically and

B Apparently isolated deoxycortico sterone excess[56]

C Congenital abnormalities of corti costeroid synthesis

1 *17α hydroxylation deficiency*[57 58]

2 11β hydroxylation deficiency[59]

3 21 hydroxylation deficiency[60]

4 Hypertension associated with some cases of Turner s syn drome[34]

D *Cushing s syndrome*[2]

E Corticosterone excess[61]

F Licorice[62 66] and carbenoxolone in duced hypertension[1 67]

V LOW RENIN HYPERTENSION WHERE NO CAUSAL AGENT IS FOUND[12 68 72]

A Mineralocorticoid excess sus pected[68 70]

B Mineralocorticoid excess not im plicated[73]

Low renin hyperaldosteronism

ALDOSTERONE SECRETING ADRENOCORTI CAL ADENOMA This is the classical form of the disease originally described by Conn[2] a benign adenoma of the adrenal cortex se creting an excess of aldosterone and giving rise to increased plasma levels of aldo sterone The effect of the elevated circulat ing aldosterone is to promote sodium re tention and potassium wasting hence total exchangeable and plasma sodium are ele vated total exchangeable and total body potassium are reduced and hypokalemia usually occurs[7] In association with the sodium retention total body water extra cellular fluid and plasma volumes are in creased[7 11 4] and there is a resultant de pression of circulating levels of renin and angiotensin II[4 6 11 74] In this syndrome therefore the aldosterone secretion is clearly not a consequence of stimulation by the renin/angiotensin system[75] indeed in our own series a significant inverse correla tion has been demonstrated between con current measurements of plasma concen trations of renin and aldosterone[11 76]

The hypertension appears to be closely related to the sodium retention and we have discussed elsewhere in some detail possible mechanisms underlying the de velopment of high blood pressure[35 76 78]

Surgical removal of the adenoma leads to a fall of aldosterone secretion rate and plasma aldosterone with consequent na triuresis and correction of the hypokalemia Plasma concentrations of renin and angio tensin II increase as the total exchangeable sodium falls and the hypertension usually, although not invariably is corrected[11 79]

The effects of spironolactone in counter acting aldosterone excess and controlling the hypertension have been clearly demon strated in this syndrome The dose of spironolactone has to be substantial (up to 400 mg per day) in view of the often markedly elevated aldosterone secretion rate With adequate therapy total ex changeable sodium and plasma sodium are reduced as are total body water extracellu lar fluid and plasma volumes Total ex changeable potassium and total body potassium increase and plasma potassium rises into the normal range[4 11 74 80] Extra cellular alkalosis is also corrected and plasma bicarbonate concentration falls Plasma levels of renin and angiotensin II rise as the total exchangeable sodium falls and sometimes abnormally high levels of renin and angiotensin are observed during treatment possibly indicating over correc tion and slight sodium depletion The effect of spironolactone on aldosterone secretion rate is variable With treatment several potential stimuli to aldosterone secretion are activated (potassium retention sodium depletion and elevation of angiotensin II) Spark and Melby[80] found that aldosterone secretion rate increased during therapy in some cases although Brown and col leagues[4 11 74] observed that it might remain unaltered indicating relative autonomy of the adrenocortical adenoma Plasma aldo sterone concentration may be elevated during therapy[11] this perhaps is partly due to an increase in aldosterone secretion partly to diminution in aldosterone meta bolic clearance possibly related to reduc tion in hepatic blood flow and partly to shrinkage of plasma volume

ADRENOCORTICAL MICRONODULAR HYPER PLASIA It is now recognized that not all cases of low renin hyperaldosteronism are due to aldosterone secreting adrenocortical adenomata In approximately 25 per cent of cases the adrenal cortices show dif fuse usually bilateral micronodular hyper plasia simple hyperplasia of the zona glo merulosa or even in a small proportion no recognizable histological change[6 11 81] It is possible in these cases that the excess of

The use of spironolactone in the diagnosis and the treatment of hypertension associated with mineralocorticoid excess

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Spironolactone is a steroidal lactone which antagonizes the actions of aldosterone particularly in distal renal tubules where it promotes sodium excretion and potassium retention. The drug is frequently employed for its diuretic actions but here we will consider its use as a specific agent in correcting the hypertension and electrolyte abnormalities of hyperaldosteronism and other syndromes of mineralocorticoid excess. For this purpose the forms of hypertension where mineralocorticoid excess has been implicated have been classified below. Clearly in some of the rarer syndromes spironolactone therapy is not appropriate and they are merely included for completeness.

Classification of hypertension associated with excess of mineralocorticoids[1]

I. ALDOSTERONE EXCESS WITH LOW PLASMA RENIN
- A. Aldosterone-producing adrenocortical adenoma ("primary aldosteronism")[2-5]
- B. Adrenocortical micronodular hyperplasia ("idiopathic hyperaldosteronism," "pseudo-primary aldosteronism")[6-12]
- C. Adrenocortical carcinoma[13, 14]
- D. Dexamethasone-responsive hyperaldosteronism[5, 28] (Glucocorticoid-remediable hyperaldosteronism)

II. ALDOSTERONE EXCESS ASSOCIATED WITH A HIGH PLASMA RENIN
- A. Malignant phase hypertension[1, 29-32]
- B. Renal artery stenosis[29-33]
- C. Severe bilateral chronic renal disease[33-35]
- D. Renin-secreting renal tumor[36-40, 112]
- E. Congenital hyperaldosteronism[1, 41]
- F. Following treatment with benzothiadiazines[42-45]

III. HYPERTENSION OF PREGNANCY[46-48] AND HYPERTENSION DUE TO ORAL CONTRACEPTIVE DRUGS[49-53, 87]

IV. NON-ALDOSTERONE MINERALOCORTICOID EXCESS
- A. 18-Hydroxy-deoxycorticosterone excess[54, 55]

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is more likely in patients with evidence of renal impairment before starting treatment [11, 80]

ADRENOCORTICAL CARCINOMA Occasional cases of hyperaldosteronism with hypertension due to a carcinoma of the adrenal cortex have been described [13, 24] It is important that this is borne in mind before embarking on long term spironolactone therapy Most examples of carcinoma have had features which should readily distinguish them from adenomata The tumors have usually been large frequently displacing the kidney on intravenous urography or arteriography fever and abdominal pain have been common and usually other corticosteroids in addition to aldosterone have been produced in excess [23]

DEXAMETHASONE RESPONSIVE ALDOSTERONISM This syndrome is probably extremely rare [26, 28] and is usually associated with hyperplasia or nodular changes in the adrenal cortex It is our usual practice before starting spironolactone to test the effect of dexamethasone in a dose of 2 mg per day for 2 weeks To date we have not seen an example of dexamethasone responsiveness

Secondary hyperaldosteronism

These syndromes are seen in association with unilateral or bilateral renal or renal artery disease [1, 29, 31, 33, 7] and in malignant phase hypertension [1, 33, 77] with or without an identifiable cause An important variety is seen in those patients with terminal renal failure treated with hemodialysis whose blood pressure is not readily controlled The hyperaldosteronism is associated with elevated levels of renin and angiotensin and in contrast to primary aldosteronism significant positive correlations of concurrent measurements of renin angiotensin I and II and aldosterone have been demonstrated [76, 73, 87, 83]

RENAL ARTERY STENOSIS In severe cases of renal artery stenosis where the malignant phase is usually present [29, 32, 78] patients may have markedly elevated levels of renin angiotensin II and aldosterone and an associated reduction in plasma and total exchangeable potassium However in contrast to low renin hyperaldosteronism the plasma and total exchangeable sodium may be reduced [29, 31, 32] Surgical relief of the stenosis may lead to correction of the hypertension and the biochemical abnormalities Clearly the hypertension is not simply due to the sodium and water retention of aldosterone excess [75] and it is postulated that the reduction in blood flow to the affected kidney causes an intense signal for renin release inappropriate to the requirements of the body The resultant high levels of angiotensin II stimulate aldosterone secretion which favors sodium retention and elevation of the blood pressure However the raised arterial pressure provokes natriuresis from the unaffected kidney and the increased levels of angiotensin II cause sodium loss from both the poststenotic and unaffected sides [89] The over all effect appears to be a slight reduction in the total exchangeable sodium It is possible that in these circumstances the elevated levels of angiotensin II are sufficient to have a direct pressor effect However in many less severe cases of renal artery stenosis with hypertension [10] the peripheral plasma concentrations of renin and angiotensin II are within the normal range [79] Even in these however it is possible that renin and angiotensin II are inappropriately high in relation to sodium status [91, 112]

MALIGNANT PHASE HYPERTENSION A very similar syndrome may be seen in malignant phase hypertension in the absence of a demonstrable renal or renal artery lesion [1, 32, 33] It has been suggested that in this situation intrarenal arterial and arteriolar lesions resulting from the malignant phase may produce a similar effect on renin secretion to that of renal artery stenosis [113] Antihypertensive therapy permits the histological lesions to heal and the elevated levels of renin angiotensin II and aldosterone revert to normal

INTRACTABLE HYPERTENSION IN TERMINAL RENAL FAILURE In the majority of patients undergoing regular hemodialysis for chronic renal failure blood pressure is readily controlled by removal of sodium and water at dialysis with restriction of sodium and water intake between dialyses In a minority however these measures are ineffective and severe intractable hypertension develops in association with very high levels of circulating renin angiotensins I and II and aldosterone [34, 36, 89] Removal of salt and water at dialysis fails to control the blood pressure resulting merely in further eleva

aldosterone is under the stimulus of some as yet unidentified trophic factor

Spark and Melby[80] found spironolactone to be ineffective in controlling the hypertension in two cases without adenoma, and suggested that such lack of response might be general in this variant of the disease and thus be the basis of a preoperative test, differentiating the adenoma and non adenoma groups Crane and Harris[82] however, obtained a good response to spironolactone in two non adenomatous patients and Brown and colleagues[11] in a more extensive series found no significant difference in the hypotensive response to prolonged spironolactone therapy in 21 patients with and 11 without adrenocortical adenoma In both adenomatous and non adenomatous groups occasional lack of hypotensive response was usually associated with evidence of renal impairment before the start of therapy This experience did, however, confirm Spark and Melby s finding[80] that the hypotensive response to preoperative spironolactone usually predicted very closely the subsequent effect of adrenocortical surgery

It is our practice to give spironolactone to within 24 hours of operation thus presenting the patient to surgery with normal electrolyte status Furthermore preoperative spironolactone may combat or minimize the development of postoperative hypoaldosteronism[114] It is emphasized that spironolactone or its breakdown products give a fluorescence in plasma very similar to that of cortisol if therefore the Mattingly test[83] is used to measure 11 hydroxy corticosteroids, a falsely high result will be given if the patient is receiving spironolactone[1,33,84] This effect takes some 14 days to clear after therapy is withdrawn

Although the response to spironolactone cannot be used in distinguishing cases with from those without adrenocortical adenoma, this distinction can be made on biochemical grounds Several workers have observed that the biochemical features of the disease are generally more marked in the adenoma group[8,10,81] plasma levels of aldosterone sodium, and bicarbonate tending to be higher and renin and potassium lower Individually, these measurements are not usually sufficient to provide a firm basis for diagnosis, but a multifactorial computer assisted technique evaluating them all simultaneously (quadric analysis) has been successfully and consistently utilized in distinguishing patients with from those without adrenocortical adenoma[81,85]

Prolonged therapy with large doses of spironolactone has been shown to be effective in a large series of patients with and without adrenocortical adenoma[11] with no tendency for the blood pressure to escape from control even after periods of up to 9 years Thus spironolactone treatment can now be offered as a reasonable alternative to the extensive bilateral adrenocortical resection otherwise required in patients shown on the basis of quadric analysis to be unlikely to have an adrenocortical adenoma Spironolactone can similarly be employed in patients unwilling or unsuitable to undergo operation Although the drug has many possible side effects in our experience these are not usually severe and in only 2 of 67 cases was it necessary to withdraw therapy[11] This contrasts with earlier statements[80] that side effects usually rendered long term therapy intolerable Epigastric discomfort following ingestion of the tablets can usually be minimized if they are taken with or after food although spironolactone is inadvisable in patients with peptic ulceration Gynecomastia occurs frequently in male patients after several months of therapy in high dosage[84] there have been occasional complaints of impotence In women menorrhagia oligomenorrhea or occasional amenorrhea occurs Other complaints have been constipation excessive sweating lassitude (especially in the early months of therapy), alopecia Raynaud s phenomenon and cutaneous pigmentation Patients unresponsive to both surgery and spironolactone generally have evidence of renal impairment a finding which is in accordance with the notion that perpetuation of the hypertension might be related to intra renal vascular damage consequent upon the raised arterial pressure[86]

Spironolactone irrespective of the hypotensive effect invariably corrects the abnormal electrolyte pattern consequently potassium supplements are not required and may indeed be dangerous Elevation of plasma potassium to abnormally high levels

droxycorticosteroids by the Mattingly technique[1,83,84]

In one case of corticosterone excess associated with an adrenocortical carcinoma in a patient with hypertension hypokalemia hypernatremia and peripheral edema a 6 day course of spironolactone 300 mg daily was ineffective[61]

Licorice extracts contain the ammonium salt of glycyrrhizic acid a substance with an aldosterone like action As a result persons who consume large quantities of licorice-containing sweets and drinks may develop hypertension with hypernatremia low plasma renin and hypokalemic alkalosis[62-66] This syndrome may be corrected by spironolactone treatment[64] A similar clinical picture may be induced by therapy with carbenoxolone[1,67] but spironolactone is contraindicated in its correction as it also blocks the ulcer healing effect

Low renin hypertension

It is now apparent that approximately 25 per cent of patients with apparently essential hypertension have low levels of plasma renin activity[69,72] It has been postulated that the suppression of renin in many of these patients may be related to excess of an as yet unidentified mineralocorticoid[68,70] This supposition is supported by the observation that a number of such cases have low levels of plasma potassium[56] and an increase in total exchangeable sodium[69] Crane and colleagues[72] treated 43 patients of this type with high doses of spironolactone and achieved a marked reduction in blood pressure in 77 per cent within three weeks whereas only 38 per cent of patients otherwise similar but with normal levels of renin showed such blood pressure reduction This and other reports[97] may be regarded as circumstantial evidence in favor of excess of a circulating mineralocorticoid in some of the low renin group In the series of Crane and associates[2] and Carey and co workers[97] measurements of 18 hydroxy DOC and DOC were not reported and it is possible that these steroids may have been present in excess in at least some cases

In this unit we have studied 10 cases of hypertension in whom the plasma renin concentration fell below the *normal range* on at least one occasion and in whom aldosterone and DOC excess *were not* found In 8 of the 10 a good hypotensive response similar to that seen in the majority of cases of primary aldosteronism was achieved By contrast *of 8 patients* with essential hypertension and plasma renin concentration persistently within the normal range only one achieved a fall in diastolic pressure to below 95 mm Hg

It appears unlikely however that all cases of hyporeninemic hypertension are associated with mineralocorticoid excess Schalekamp and colleagues[73] studied 50 cases of essential hypertension excluding those with hypokalemia and found no increase in plasma and extracellular fluid volumes in the patients with low plasma renin in comparison with patients with normal levels They did observe however that suppression of plasma renin increased in frequency with advancing years and this led to the suggestion that patients with essential hypertension and normal levels of renin may develop renin suppression as they grow older It may well be that the 23 per cent of patients in the series by Crane and colleagues[72] who had low levels of plasma renin but who did not respond to spironolactone were of this type

Spironolactone in essential hypertension

Spironolactone does have a significant albeit small hypotensive action in some cases of essential hypertension the effect being comparable only with that of thiazide diuretics[98-102] The dosage of spironolactone employed in most series has generally however been smaller (150 to 200 mg per day) than that given in syndromes of definite mineralocorticoid excess (see above) The potency of large doses of spironolactone in essential hypertension remains to be fully assessed[103] There have been few clinical trials but Crane and colleagues[72] and Carey and associates[97] demonstrated a much less impressive antihypertensive effect in patients with normal *renin than* in those presenting with low renin hypertension

On present evidence both spironolactone and thiazides while possibly *effective* alone in mild to moderate hypertension require the addition of more potent agents in the treatment of severe hypertension[104] Thiazides and spironolactone when used in combination may show some potentiation

tion of renin and angiotensin II with aggravation of the hypertension It has been demonstrated in patients of this type that renin and angiotensin II levels are disproportionately elevated in relation to the normal or only slightly reduced exchangeable sodium[91,113] and thus circulating angiotension might well be sufficient to have a direct pressor effect It is suggested that the grossly diseased kidneys provide an appropriate signal to renal release in relation to total exchangeable sodium, and that this signal is intensified when salt and water are removed at dialysis Bilateral nephrectomy is followed by a steep fall in circulating renin and angiotensin II to very low levels and usually prompt control of the arterial pressure[35,53,89]

SPIRONOLACTONE IN SECONDARY HYPERALDOSTERONISM Although it may be of value in correcting hypokalemia spironolactone therapy has been generally found ineffective in controlling the hypertension in syndromes of secondary hyperaldosteronism[1,33,35,50,53] This is hardly surprising as aldosterone excess does not appear to be the principal cause of the hypertension In contrast to primary hyperaldosteronism in which total exchangeable sodium is elevated and can be corrected by spironolactone therapy, in secondary hyperaldosteronism total exchangeable sodium is normal or reduced and spironolactone treatment serves only to lower total exchangeable sodium further and therefore usually to intensify the basic abnormalities Thus while a slight and sometimes helpful hypotensive effect can be achieved other forms of therapy need to be employed to achieve a full therapeutic effect

Pregnancy oral contraceptive therapy

The renin/angiotensin/aldosterone system appears not to be causally related to the hypertension of pregnancy[46,48] In normal pregnancy renin renin substrate angiotensin II, and aldosterone increase markedly whereas in pre eclamptic toxemia, all four components are significantly lower than in normal pregnancy, although (apart from angiotensin II) often remaining above the non pregnant range[48] Diuretics are frequently used in the treatment of this condition when edema is present and spironolactone has been found to be as effective as benzothiadiazines[92] However, the rational basis for using an aldosterone antagonist in this situation is uncertain and such therapy cannot on present evidence be recommended

The hypertension produced in some women taking oral contraceptives does not appear to be consistently associated with aldosterone excess[49,53] and is best treated by stopping the tablets

Spironolactone in syndromes of mineralocorticoid excess other than aldosterone

Genest and Nowaczynski[54] and Melby and associates[55] have reported increased secretion of 18 hydroxydeoxycorticosterone in some patients with hypertension, suppressed plasma renin activity and normal or reduced aldosterone secretion The hypertension in some of these was reported to have been corrected by administration of spironolactone in high dosage[55]

It has been shown in rats[93] and in man[94] that the spirolactones block the salt retaining actions of deoxycorticosterone acetate (DOCA) as well as of aldosterone Since DOCA is rapidly hydrolyzed to deoxycorticosterone (DOC) in vivo[95] spironolactone might be expected to be effective in clinical hypertension associated with DOC excess

Brown and colleagues[56] found that of 21 patients with hypertension associated with suppression of plasma renin 6 had consistently elevated plasma concentration of DOC although plasma aldosterone was normal as were 11 hydroxycorticosteroids and their response to synthetic corticotrophin The mean plasma potassium in this group of patients was low Five of the 6 patients were treated with high doses of spironolactone and in all cases there was a significant hypotensive response which was marked in three Hypokalemia was in all instances corrected during therapy These observations confirmed that some cases of low renin hypertension could indeed have an excess of a previously unidentified mineralocorticoid

In Cushing s syndrome specific therapy to correct the steroid excess is indicated[96] and spironolactone has not as far as we are aware been generally advocated in the treatment of the hypertension and electrolyte abnormalities We have in one patient used it successfully to correct hypokalemia Caution is necessary as spironolactone will interfere with the measurement of 11 hy

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of effect and there may be an additional benefit in that the spironolactone will correct hypokalemia induced by thiazides [98]

There is some evidence that in essential hypertension, the salt and water diuresis induced by thiazides is short lived whilst the antihypertensive action persists [101] After prolonged treatment plasma and extracellular fluid volumes[105, 106] and cardiac output[107] have all been described as returning to pretreatment levels More recently however [45] it has been reported that plasma volume contraction persists although this may not entirely account for the hypotensive action It has been postulated that the thiazides may exert some of their hypotensive action by a peripheral vascular mechanism independent of the diuretic effect and there is evidence that spironolactone shares such a mechanism[108] with thiazides This may explain why in essential hypertension where there is no demonstrable salt or water excess spironolactone is only partially effective, in contrast to the usually marked response seen in low renin hyperaldosteronism If a patient with apparently essential hypertension develops a very marked reduction in blood pressure while taking spironolactone the diagnosis of mineralocorticoid hypertension should be considered

Mode of action

As spironolactone specifically blocks the receptor sites of aldosterone, it is to be expected that this agent would be most effective where excess of aldosterone is the primary cause of the hypertension However spironolactone has been shown to be equally effective in some syndromes of mineralocorticoid excess where the aldosterone concentration is normal but in these syndromes total exchangeable sodium is increased also

Where the total exchangeable sodium is not elevated a less powerful hypotensive effect is likely although it is perhaps not surprising that some striking successes may occasionally be achieved Early reports of the use of amiloride a potassium conserving diuretic which acts independently of the presence or absence of aldosterone indicate that it may produce similar correction of hypertension plasma electrolytes, and body spaces to that achieved by spironolactone, both in cases of aldosterone secreting adenoma and in non aldosterone mineralocorticoid excess [109, 110] Whether such non specific potassium-conserving natriuretic agents[111] will be as effective as spironolactone remains to be determined

Conclusions

While there is increasing interest in the use of spironolactone as a diagnostic and therapeutic agent in different forms of hypertension the multiple side effects although not usually severe require that high dose therapy should not be embarked upon lightly Lower doses however may be a very effective addition to other hypotensive agents and probably are associated with less unpleasant symptoms Extreme caution is necessary in patients with renal impairment since uremia may be aggravated and dangerous hyperkalemia provoked

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Peripheral arterial occlusion in patients with acute coronary heart disease

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Relatively little is known about the epidemiology of peripheral arteriosclerosis obliterans Although it is associated with many of the same risk factors as coronary and cerebrovascular disease accurate prevalence figures in differing populations are not available In the past case finding in peripheral arterial disease has been hampered by lack of a precise definition of normality and in many instances reliance has been placed solely on a history of intermittent claudication However there are now sufficient data from normal subjects to establish clinical criteria for the presence of asymptomatic arterial occlusion[1,2] The purpose of the present study was to apply these criteria to patients with acute coronary heart disease in order to assess the co prevalence of atherosclerosis in the extremities and the heart

Material and methods

One hundred consecutive patients admitted to the Coronary Care Unit of the Coney Island Hospital with acute myocardial infarction but no evidence of hypotension or significant peripheral edema were examined carefully for the presence of peripheral arterial disease The diagnosis of acute myocardial infarction was based on characteristic symptoms in association with established electrocardiographic criteria and/or elevation of serum enzyme levels (SGOT LDH and CPK) Every patient in the study had an abnormal electrocardiogram

A careful history was obtained with reference to the following previous myocardial infarction symptoms compatible with congestive heart failure angina pectoris hypertension diabetes mellitus intermittent claudication cigarette smoking

Arterial examination in each case was performed independently by two examiners between the second and fourth hospital days The radial ulnar femoral popliteal dorsalis pedis and posterior tibial pulses were graded as normal or

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Table I Summary of clinical data

Group	No	No of females	Mean age (yr)	History of hypertension	History of smoking
Definite peripheral arterial occlusion	55	24	62 (43 83)	18 (33%)	37 (67%)
Normal peripheral arterial examination	45	6	59 (41 72)	19 (42%)	26 (58%)
Total	100	30	60 (41 83)	37	63

absent and oscillometric readings were obtained at each ankle With the patient lying supine systolic blood pressures were obtained by palpation of the radial pulses with a sphygmomanometer cuff around the arm and of both the dorsalis pedis and posterior tibial pulses (if present) with the cuff placed on the lower third of the calf Systolic pressure was taken as the minimum pressure required to obliterate the pulse Fifteen normal subjects (ages 24 to 31 years) were examined in the identical fashion

All pulses were repeatedly examined by both observers until definite agreement could be reached The posterior tibial pulse was sought with the patient supine and relaxed and the observer seated on the side being examined The entire area under the medial malleolus was palpated and this maneuver was repeated with the foot externally rotated before the posterior tibial pulse was declared absent The entire anterior surface of the foot was palpated for the dorsalis pedis artery in positions of flexion and extension

The following findings were considered diagnostic of arterial occlusion (1) absence of one or both posterior tibial pulses (2) absence of radial and ulnar pulses in a wrist, and (3) a posterior tibial artery blood pressure at least 20 mm Hg lower than that of the radial arteries

Blood sugar level at the time of hospitalization serum cholesterol concentration, and hematocrit were also recorded for each patient

Results

Table I summarizes the data for 55 patients with definite peripheral arterial occlusion and for the 45 patients who did not meet the criteria for this diagnosis Mean age was 60 years and 70 per cent were men Of the entire series of 100 patients 63 had been smoking for a mean of 31 years 21 had diabetes mellitus and 34 had a history of hypertension At least one of these 3 factors was present in 85 per cent of these patients with acute myocardial infarction Eighty eight per cent had one of these factors and/or definite peripheral arterial disease

There were statistically significant differences between the sexes in this series Twenty four of 30 women (80 per cent) had definite peripheral arterial occlusion compared to 31 of 70 men (44 per cent) ($P < 01$) Eighty four per cent of men and 40 per cent of women were cigarette smokers ($P < 01$) Thirty three per cent of women had a history of diabetes mellitus as compared to 16 per cent of the men but this difference was not statistically significant (P between 05 and 10) Mean age and serum cholesterol levels were virtually identical for men and women

A history of diabetes mellitus was present in 18 patients (29 per cent) with extremity involvement whereas 3 of 45 patients (7 per cent) were diabetic in the group without peripheral arterial occlusion ($P < 01$) Of the 21 diabetics 4 had been treated with insulin 12 with oral hypoglycemic agents and 5 with diet alone No significant difference was found between the 2 groups in regard to age history of smoking or hypertension blood sugar or serum cholesterol level hematocrit or mean blood pressure while in the coronary care unit

A previous history of heart disease was obtained from 51 patients (angina pectoris

History of diabetes	Mean serum cholesterol (mg/100 ml)	Mean blood sugar (mg/100 ml)	Hematocrit	Previous heart disease	No with serum cholesterol over 300 mg/100 ml
18 (33 %)	228	151	44%	31	6
3 (7)	243	148	41%	20	4
21	234	150	42%	51	10

in 47 previous myocardial infarction in 31 and congestive heart failure in 14) Of the 49 patients suffering their first symptoms of heart disease 24 (49 per cent) had definite peripheral arterial occlusion Patients with and without a history of previous heart disease were similar in all other parameters measured

The distribution of abnormalities in patients meeting the criteria for peripheral arterial occlusion is given in Table II In 44 cases one or both posterior tibial pulses were missing Ten patients were diagnosed on the basis of low blood pressures in the posterior tibial arteries Seven of these 10 also had either missing dorsalis pedis pulses or low blood pressure readings on palpation of that artery A history of intermittent claudication was present in 18 (33 per cent) of this group Forty seven patients had oscillometric readings below 2 units and the other 8 patients had a normal blood pressure in the anterior tibial artery of each leg (as measured by dorsalis pedis palpation)

In addition to the 55 patients with definite arteriosclerosis of the extremities 7 patients (6 men and 1 woman) had asymmetry of their dorsalis pedis pulses In 3 a dorsalis pedis pulse was unilaterally absent 3 others had a 25 to 50 mm Hg pressure difference between the 2 dorsalis pedis arteries the lower one being well below arm pressures and 1 had absence of one dorsalis pedis pulse and a low pressure in the other

In the 15 normal subjects tibial artery blood pressure readings were never lower than those of the upper extremities Fifty nine of the 60 tibial arteries had pressures 10 to 25 mg Hg higher than those of the upper extremities

Table II Findings in 55 patients with peripheral arterial occlusion

Finding	*No*
Intermittent claudication	18
Absent posterior tibial pulse	44
Pulseless wrist	1
Low posterior tibial blood pressures (both pulses palpable)	10
Low or absent oscillometric readings	47
Femoro-popliteal arterial occlusion	21

Discussion

The accessibility of the peripheral circulation to physical examination affords an opportunity to make a clinical diagnosis of asymptomatic arteriosclerosis Previous work has shown that a missing posterior tibial or radial pulse is virtually always pathologic[1 2] Dorsalis pedis pulses have been reported missing in 5 to 12 per cent of normal subjects but unilaterally in only 3 to 6 7 per cent[1 2] In normal individuals intra arterial blood pressure measurements are identical in the brachial and femoral arteries With a sphygmomanometer cuff blood pressure is often recorded artificially higher in the lower extremities because of their wider girth but their pressures should never be lower than those of the arms[4 5] This was confirmed by the findings in our normal subjects Oscillometry although only semiquantitative is useful for confirming the presence of peripheral arterial disease in many cases (47 of 55 in the present study) The reading decreases as perfusing pressure in the leg falls but the latter will generally be relatively unaffected if one tibial vessel remains uninvolved[4]

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diagnosing coronary artery disease Since 88 per cent of the patients had peripheral arterial disease and/or a history of smoking diabetes or hypertension the value of these factors in evaluating a patient with atypical chest pain is obvious Clearly examination of the peripheral arteries is a useful screening procedure for the identification of individuals prone to coronary heart disease they can then be studied further with a view to eliminating some of the risk factors

Summary

One hundred consecutive patients with acute coronary heart disease were examined carefully for the presence of peripheral arterial occlusion In addition to pulse palpation blood pressures and oscillometric recordings were obtained in the lower extremities Fifty five had definite arterial occlusion and seven had findings strongly suggestive of peripheral arterial disease Only one third of the patients with arterial occlusion gave a history of intermittent claudication One half of the patients with no previous cardiac history already had signs of peripheral arteriosclerosis The data suggest that examination of the peripheral circulation is a useful screening procedure for the identification of individuals prone to coronary heart disease

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Since the histopathology of atherosclerosis in the femoral and popliteal arteries is indistinguishable from coronary artery disease, it is not surprising that peripheral arterial and coronary heart diseases are intimately associated. Although epidemiologic studies on incidence and prevalence have identified risk factors common to both, such as hyperlipidemia,[6] diabetes mellitus, and cigarette smoking,[7,8] there is a dearth of data concerning the frequency of peripheral arterial disease. The National Center for Health Statistics has published age-related estimates of the prevalence of coronary disease[9] and hypertension[10] but offers no comparable statistics for peripheral arterial occlusion.

Most of the available information is confined to prevalence and incidence of intermittent claudication. Mahmoud[11] estimated that 6 per cent of men and 3 per cent of women between the ages of 55 and 74 have claudication. Kannel and co-workers,[12] in following the Framingham Population Study Group, noted that the risk of developing claudication was 8 to 10 times as high in people with coronary heart disease as those with no heart disease. Men with claudication developed coronary disease 3 times as frequently as those without this symptom and women 9 times as frequently. McDonald[13] found a common coexistence of angina pectoris and intermittent claudication in 137 patients. Boyd[14] noted non-fatal myocardial infarction within 5 years of the onset of claudication in about 20 per cent of 1,440 patients.

Intermittent claudication is likely to identify only a fraction of all patients with peripheral arterial disease since this symptom is usually not present unless there is involvement of the larger arteries. Furthermore, claudication will occur in a mild case of peripheral arterial disease only if the patient is in the habit of walking a considerable distance without stopping. The presence of intermittent claudication in only one third of our subjects with definite peripheral arterial occlusion is striking proof of the insensitivity of this symptom as an epidemiologic tool.

The sex distribution of peripheral arterial occlusion in patients with coronary heart disease is difficult to explain. A significantly higher propensity for generalized arterial disease in females found in this series and the Framingham Study[12] could not be explained by any difference in mean age, serum cholesterol level, smoking history, or prevalence of diabetes mellitus. Perhaps it is a reflection of a fundamental difference between men and women in the nature of atherosclerosis. Women who develop coronary heart disease in middle age may represent a group with a strong genetic predisposition to atherosclerosis and therefore might tend to have wider involvement of the arterial system, whereas this disease process in men may be more or less a natural result of the aging process.

The much higher prevalence of diabetes in patients with extremity involvement is consistent with the known susceptibility of diabetics to peripheral arteriosclerosis obliterans. The latter is estimated to be 11 to 40 times as frequent in the diabetic as in the non-diabetic population.[15,16]

The results of the present study suggest that the majority of patients who are hospitalized with acute coronary heart disease already have clinically detectable peripheral arterial disease. In addition to the 55 patients with definite criteria for this diagnosis, 7 other patients had marked discrepancies between their 2 dorsalis pedis pulses—findings suggestive although not diagnostic of arterial occlusive disease.[17] Forty-nine patients gave no history of angina, previous myocardial infarction, or congestive heart failure, and it is reasonable to presume that they were having their initial clinical manifestations of heart disease. Although it is possible that careful examination prior to their myocardial infarction would have revealed evidence of cardiomegaly or gallop rhythm, heart disease would probably have gone undetected in most cases by history and physical examination. On the other hand, significant atherosclerosis could have been diagnosed before cardiac symptoms occurred in about half these patients with close attention to the peripheral pulses. The incorporation of blood pressure measurements in the lower extremities appears to offer an advantage over pulse palpation alone since peripheral arterial disease was diagnosed by blood pressure readings alone in 10 patients.

The results of this survey suggest that certain historical information is helpful in

subjected to cardiac catheterization for suspected anginal syndrome Indeed a small number of patients with documented myocardial infarctions have normal coronary arteriograms

Evaluation of the function of the left ventricle is essential in the proper selection of candidates Operative and late death as well as the effectiveness of surgery is closely related to the performance of the left ventricle The size and shape of the chamber its contractility filling pressure and output are parameters usually measured By means of *left ventriculography the dynamic* changes of the contracting ventricle can be appreciated and areas of reduced *or absent* contractility delineated Associated mitral *regurgitation can* be assessed and ventricular volumes calculated The ejection fraction that is the amount of the diastolic volume reduced with each beat is inversely proportional to the operative and late mortality rate of surgery As the ejection *fraction* falls and other evidence of poor left ventricular function appears the risks of operation increase Ventricular dysfunction is one of the most important determinants of patient survival An operative mortality rate of less than 5 per cent in patients with good ventricular function can *be 30 to 0 per cent in the presence of severe* cardiac enlargement and failure

Anginal syndrome Anginal syndrome refractory to optimum medical treatment constitutes the principal indication for bypass surgery today Refractoriness is an arbitrary term which must be applied to each particular patient It is affected by the tolerability of his symptoms and its effects upon his work activities and total life style Mild recurrent chest discomfort readily responsive to medications such as nitroglycerine may be tolerated by many *individuals* Severe recurrent exertional pain nocturnal and rest angina unrelieved *by medical management generally* is not acceptable

The presence of right coronary left anterior descending and left circumflex obstructions singly or in combination in a patient with intractable angina is an indication for operation Complete or partial relief of symptoms may be expected in 80 to 90 per cent of these cases

Unstable angina Preinfarction angina impending myocardial infarction acute coronary insufficiency *intermediate coronary* syndrome and crescendo angina are terms applied to an *unstable anginal syndrome* manifest by rapidly progressively severe and protracted chest pains Early reports of poor prognosis and progression to infarction *in this group have been questioned* by more recent studies Differences *in patient selection and* availability of observation and management in coronary care units may be *factors in* their low incidence of early infarction Lack of arteriographic confirmation in most instances makes further comparisons even more difficult When angiographic data are available the distribution and extent of stenotic lesions is similar in both chronic stable and acute unstable angina

Most patients with acute development of angina will respond to rapid institution of bed rest and medical therapy Those with sudden exacerbation of chronic angina and those in whom angina persists despite intensive management should be considered high risk patients and evaluated by arteriography for possible emergency bypass surgery

Chronic congestive heart failure Chronic heart failure is the predominant manifes*tation of many patients with coronary* occlusive disease Bypass surgery with and *without resection of aneurysmal portions of* the left ventricle has had little effect in *regard to improvement in ventricular fill*ing pressures contractility and cardiac output Surgical mortality rate is high and one year survival low

Some patients with significant anginal syndrome and a moderately reduced left ventricular ejection fraction might be considered for bypass surgery despite the higher risks of operation Individuals with little or no angina and severe impairment of left ventricular function should not be subjected to coronary bypass surgery with the expectation of meaningful clinical im*provement*

Acute myocardial infarction Documented acute myocardial *infarction* generally has been considered a contraindication to surgery Established muscle *necrosis will* not be reversed by revascularization and the risks of operation are excessive *On the* other hand supported by animal experi

Indications for aortocoronary artery bypass surgery

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Aortocoronary artery bypass grafts for coronary occlusive disease clinically introduced in 1967 have reached epidemic proportions As the current trend mushrooms in 1973 we should anticipate many more procedures than the estimated 20 000 performed in the United States last year

There is no question of the efficacy of coronary bypass surgery for the relief of angina in selected patients Whether future myocardial infarctions will be prevented and life prolonged is not yet clearly demonstrated In this regard a randomized prospective study already is under way within the Veterans Administration Hospital system and a cooperative investigation by a number of large medical centers is being organized by the National Heart and Lung Institute Hopefully these and the objective results of other operating groups will provide a meaningful therapeutic evaluation of the operation on the course of arteriosclerotic coronary occlusive disease in the future

At the present time there is unbridled enthusiasm and acceptance of the procedure on the one hand concern and caution on the other The controversy has been a favorite subject for editorials in medical journals and the lay press has given it abundant coverage Television and national periodicals have informed the public of its potential and increased the pressures of patient demand

Objective evaluation of the effects of surgery vary depending upon the specific technics of the procedure selectivity of patients effective follow up study and the natural course of the disease There is a tremendous emotional bias in any life threatening situation and the possibility of amelioration of a destructive process by an aggressive approach even if not completely proved can be appealing to the afflicted patient and his physician It is in this emotionally charged atmosphere that the physician must decide if his patient is or is not a candidate for coronary bypass surgery today

Coronary arteriography with demonstration of significant proximal large vessel occlusion is paramount in the consideration for surgery Obstruction generally is considered significant when the reduction in size of the lumen is greater than 75 per cent Visualization of normal arterial distribution distal to the stenosis is desirable but not essential At operation patent distal vessels not apparent angiographically may be found suitable for bypass grafting Lack of coronary occlusive disease may be found in 15 to 27 per cent of various series of patients

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therapy and the presence of severe angina in most of the patients would seem to warrant consideration for early operation This lesion is not common occurring in less than 3 per cent of patients undergoing coronary arteriography and experience with surgery is not extensive Further objective evaluation is necessary particularly since left main arterial stenosis is almost never a solitary occlusive process

Asymptomatic patients In general asymptomatic patients despite documented coronary occlusive disease are not operated upon except under certain special circumstances Coronary arteriography in the assessment of valvular aortic stenosis may disclose morphologically significant obstructions in patients without angina Coronary bypass is not performed routinely unless there is difficulty in weaning the patient off the pump-oxygenator after prosthetic replacement of the valve or there is severe compromise of the coronaries with poor ventricular perfusion and anticipated low output failure in the early postoperative period Similar situations may arise during ventricular aneurysmectomy and if feasible revascularization using one or more grafts may be attempted

There is inadequate information as regards the benefits of surgery in the asymptomatic patient with uncomplicated prior myocardial infarction or demonstrable limited coronary artery disease without infarction Prediction of impending myocardial infarction or sudden death in the asymptomatic patient is not yet possible As high risk factors are identified in the natural course of the disease and further correlations are made with coronary arteriography and left ventricular function studies perhaps a more liberal selectivity of candidates for surgery will follow

Risk factors Hypertension smoking hypercholesterolemia and hyperlipidemia have been associated with acceleration of coronary atherosclerosis The over all yearly mortality rate of 3 to 4 per cent in patients with angina is increased to 8 per cent in the sub group with high blood pressure and advanced electrocardiographic abnormalities Cardiomegaly and congestive heart failure adversely affect the prognosis

With coronary arteriography we can attempt correlation of survival with distribution and extent of arterial stenosis Multiple vessel disease particularly involving the left anterior descending branch worsens the prognosis Approximately 95 per cent of patients with single vessel disease have a two year survival only 65 to 75 per cent with two and three vessel involvement live that long The importance of coronary collateral circulation and progression of obstructive lesions are variables with insufficient data for meaningful evaluation at this time

As increase in vascular stenoses and reduction in left ventricular function influence the natural history of coronary arterial disease these same factors increase the operative risks as well The intraoperative and postoperative mortality rate and infarction rate are higher in those patients requiring multiple bypass grafts and in those with ventricular dysfunction

In addition to the surgical mortality rate ranging from 3 to 10 per cent we must consider the effectiveness of operation The patency of saphenous vein aortocoronary grafts is in the range of 80 per cent after two years A one year patency of 97 per cent has been claimed for internal mammary artery bypass a procedure requiring longer operating time and with an obviously limited supply of vessels for grafting

Conclusions

Adequate statistically significant randomized data is not yet available to determine the effect of aortocoronary bypass grafting on the natural course of occlusive coronary atherosclerosis Large prospective studies under way or in the planning stage may help define the influence of surgery upon future myocardial infarction and longevity

There is no doubt of the relief of angina in about 85 per cent of patients undergoing operation In the absence of left ventricular failure operative mortality rate is low and if angina is incapacitating and unresponsive to medical management surgery should be considered Left main coronary lesions unstable angina with acute unrelieved exacerbation and myocardial infarction with cardiogenic shock are high risk situations in which operation if feasible would be recommended

Bypass surgery has been disappointing

mentation, marginal areas may be improved and the extent of necrosis may be reduced if the vascular supply is restored within three hours of occlusion

Patients developing coronary occlusion during or shortly after coronary arteriography have been operated upon satisfactorily within hours of the event However this surgical experience with persons sustaining coronary occlusion in a hospital setting cannot be applied to those admitted with myocardial infarction which occurred even a few hours prior to admission The further delay inherent in the necessary preoperative assessment by cardiac catheterization would be enough to preclude the possibility of reversibility of the developing myocardial necrosis At the present time surgery for uncomplicated acute myocardial infarction cannot be recommended

Continued angina during the course of acute myocardial infarction may be considered a variant of the unstable anginal syndrome It would suggest additional areas of ischemia in jeopardy If this is severe and is unresponsive to conservative measures the possibility of surgical intervention should be evaluated by coronary arteriography The risk of additional infarction might outweigh that of operation in these patients with otherwise uncomplicated acute myocardial infarction

Acute myocardial infarction with cardiogenic shock The high mortality rate in the ninety percentile range associated with the cardiogenic shock of acute myocardial infarction has prompted aggressive treatment in several small series of patients Mechanical circulatory assistance with an intra aortic balloon pump has been effective in some instances but the mortality rate remained about 80 per cent This device has been used to support patients in shock during coronary arteriography and left ventriculography in evaluation for myocardial revascularization All 44 studied under these circumstances at the Massachusetts General Hospital had stenosis of the left anterior descending artery The right coronary was obstructed in 77 per cent and triple vessel disease observed in 41 per cent Akinesis or dyskinesis of the anterolateral wall of the left ventricle was demonstrated and when associated with no perfusion, revascularization surgery was unsuccessful Eight patients of 22 (36 per cent) with some visible arterial perfusion of akinetic regions survived aortocoronary bypass procedures

Only one angiographically related death in this series of 44 high risk patients indicates the feasibility of assessment for surgery under these conditions Those with destruction of more than 40 per cent of the left ventricle and poor regional arterial perfusion are unlikely to survive operation Immediate survival of patients with less necrosis may be promising but long term benefits are not yet established

Evaluation of the patient with acute myocardial infarction and shock requiring mechanical circulatory assistance and consideration for bypass grafting seem reasonable in this group with such a grave prognosis

Left main coronary artery obstruction Significant left main coronary stenosis places both anterior descending and circumflex branches in jeopardy and may compromise almost the total blood supply of the left ventricle In most instances this is not an isolated lesion but is accompanied by double and triple vessel disease in the proximal left branch vessels and right coronary artery

A higher risk of coronary arteriography has been reported with a 10 to 15 per cent mortality rate Caution in study has been advised in patients with severe angina, strongly positive stress tests or calcification in the region of the left main trunk Visualization of the right coronary first may demonstrate collateral filling of the left coronary system Then a non selective left aortic sinus injection of contrast medium may adequately delineate the left main obstruction without the dangers of compromise of the lumen by selective introduction of the catheter into the coronary ostium This will be important to recognize lesions of the ostium which may not be appreciated with the catheter tip already within the coronary arterial lumen Finally cautious selective left coronary arteriograms can be accomplished for more detailed analysis

There is a higher surgical risk in this group averaging about a 12 per cent mortality rate A poor prognosis

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Bypass surgery has been disappointing

in the treatment of chronic congestive heart failure On the other side of the spectrum operation has not been proved better than medical observation in the asymptomatic patient with old myocardial infarction Acute uncomplicated myocardial necrosis will not be reversed by surgery except possibly in the few special circumstances of coronary occlusion during coronary arteriography In the light of our present knowledge there is little justification for aortocoronary bypass surgery in these three groups

As our experience with coronary arteriography and surgery increases perhaps we may liberalize the indications for operation We must continue our objective evaluation of this new therapeutic modality and not finalize its role in the management of occlusive coronary atherosclerosis until its effects upon the natural history of the disease are established

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Annotations

Study of man, himself

No other animal or living thing has been studied as extensively as man. Man is intensely interested in himself, be he normal or diseased. However, in spite of extensive investigation of many sorts, there remain much to be learned about man by man. To know more about man, investigations must be conducted directly on man. Extrapolations from studies of other animals to man are not sufficient. The study of plants and other animals is extremely important and absolutely necessary even for a better understanding of man and his reactions. Nevertheless, investigation must be conducted on man himself. For example, diseases peculiar to man such as sickle cell anemia, certain inherited metabolic diseases, angina pectoris, psoriasis, and other dermatologic states, obstetrical problems, allergic diseases such as asthma, psychiatric states such as schizophrenia, neurasthenia, urologic states such as enuresis, prostatism, and many others too numerous to even attempt to list must be studied on man.

Realizing that there is a need to study man, efforts must be made to avoid injury to man under study. Therefore, committees have been established to make certain man is not injured when subjected to research. This is good. However, it is unfortunate for many reasons that a committee for review of research plans for the study of man is necessary. A committee can have beneficial or detrimental influences on the study of man. And unfortunately, too often some members of the committee have had absolutely no experience or very little experience with research on man.

Also, too often it is not fully realized that it is the investigator who really counts when considering the quality of the research and the subject's safety. A good, considerate, thoughtful, and humane physician *will not* subject a person to investigations which are hazardous. An investigator's attitude and approach to research on man can be judged best by his past performance, including highly technical and scientific research on man as well as the use of new, yet untested drugs and procedures, diagnostic and therapeutic (medical and surgical). Whether or not it is ethical or proper to charge a fee to those who are subjected to new and nonestablished diagnostic or therapeutic procedures is questionable. I think it is not proper. Nevertheless, at one time or another these various often hazardous procedures and new drugs must be studied in man. Again, what is expected to happen and what actually happens are dependent entirely on the person responsible for the study.

Those who are primarily interested in man and who have devoted considerable effort in studying man know how delightful and satisfying it is to study man. The mere fact that the investigator can communicate directly with his subject during investigations offers tremendous advantages in obtaining data during the course of investigations. This is readily realized when studying pain. Man is the best animal to study in the conscious state. This type of study can seldom be done in other animals since the animals usually must be anesthetized merely to keep them quiet for recordings. Indeed, the anesthesia introduces an important and unknown variable. The psychic state of even conscious animals is difficult, if not impossible, to measure.

The human subject, when handled properly by the investigator, enjoys being studied and willingly participates, making the study his contribution to knowledge and for the improvement of the welfare of mankind. Man must be studied to obtain direct answers concerning man; he must be studied directly. But the researchee's welfare in every respect depends upon the researcher. It is a tremendous and invaluable privilege for the researcher to be permitted to study man. Let us not abuse that privilege under any circumstances. And remember, there is no need for haste; studies on man must be safe.

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Longevity of athletes

The confusing statistics on the longevity of athletes can probably be best understood by recognizing the different somatotypes of the athletes involved in the various sports.

Athletes come in all sizes and shapes, filling every band of the somatotype spectrum from the ectomorphic marathoner (the average height and weight of 75 winners of the Boston Marathon is 5 ft. 6 in. and 130 pounds) to the endomorphic channel swimmer (who may attain 40 per cent body fat). Along this continuum you find the ectomesomorphic basketball players, move on to crewmen, and then

on to the endomesomorphic football players and weight lifters Further into the endomorphic scale are baseball players and golfers

Studies on the general population have already indicated that certain somatotypes especially the endomesomorphs have a shorter life span in our present culture Spain and co-worker findings[2] as well as the Framingham results[3] point toward this type s constitutional susceptibility to what Biorck[4] has called the disease of our century coronary heart disease

This may be genetically programmed or may simply be that the reactions to stress of the endomorph —i e socialization—and the mesomorph—i e action—are hazardous in present day society The twin dangers of lipid affluence and an egalitarianism which allows no excuse for failure provide a perfect cultural medium for the endomorphic tendency to overindulge and the mesomorphic appetite for aggressive action

The ectomorph who leans to withdrawal and asceticism tends to live longer In times past he was more susceptible to tuberculosis and infection and his life span was therefore short But present day killers he handles well

Given this information one can understand why Prout[5] found that oarsmen live more than six years longer than randomly selected classmates why Karvonen s[6] cross country skiers outlived the national average by seven or more years

One can also realize why Schnorr [7] lumping all Danish champions together discovered that having attained the age of 50 years they merely lived out the normal Danish life span

And one can see clearly why Largey [8] scanning through Who Was Who in American Sports discovered trackmen lived longer by 14 years than football players a finding confirmed by Polednack s[9] extensive survey of 6 303 Harvard students

Winning a letter might add years to your life reported Polednack—but only if it was in a minor sport [9] Major sport athletes died significantly earlier than non athletes from coronary heart disease and perhaps earlier and oftener from tumors All this information then falls into place The differences detected by Prout [5] Schnoor [7] Largey [8] and Polednack[9] are simply the tendency of the population to have different life spans based on the reaction of their body builds with their environment

The muscularly aggressive ex football players are statistically susceptible to cardiovascular disease to just that degree shared by their muscular aggressive non football playing counterparts Onlookers who share in the magnificent physical and psychological attributes of crewmen will share in their extended life span Thin small boned people represented in sports by distance runners are longer lived than the average for reasons already cited

None of these studies incidentally claim any information on continuing athletic activity It would be best to assume that there was little or none Studies in England a much more athletically inclined country disclosed that only 10 per cent of married men aged 23 to 30 continued with regular activity [10]

We now know that ex athletes seem to live as long as and no longer than non athletes of the same body build

What we need to know is whether athletic activity continuing through middle age will modify or maximize this genetically programmed longevity quotient Will the perennial athlete outlive the ex athlete of the same somatotype that is?

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Dopamine test for the diagnosis of coronary insufficiency

The limits of the exercise test for the diagnosis of coronary insufficiency are well known We[1] have recently given evidence that infusion of isoproterenol is particularly useful for the diagnosis of coronary insufficiency in the absence of electrocardiographic (ECG) signs of the disease at rest Similar results have been obtained by Wexler Kuritzky and Simonson [2]

Better results have been obtained by our group with dopamine [3] In contrast to isopropil norepinephrine dopamine has very little effect on the heart rate furthermore at the dosage that we used it

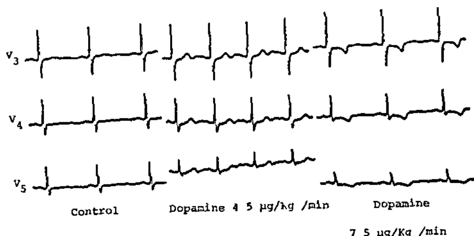


Fig 1 Effects of dopamine infusion on the ECG in a case of coronary artery disease There is an evident initial transient improvement which is followed by ischemic changes of the ST segment.

does not increase the ventricular excitability and the peripheral vascular resistance

As we know its primary cardiac effect is an increase in cardiac contractility and cardiac output secondarily it increases the myocardial consumption of oxygen and the coronary blood flow[4]

Our method is to use an intravenous administration of dopamine at an initial infusion rate of 4 5 µg per kilogram of body weight per minute The infusion rate is then raised 1 5 µg per kilogram of body weight per minute every five minutes until a systolic blood pressure 50 per cent higher than the control value is achieved

The test is stopped immediately in case subjective symptoms appear or if there are ECG signs of coronary insufficiency The dopamine test has been compared with the cycloergometer test in supine position with increasing work load Three groups of subjects have been studied The first group consisted of 49 volunteers free of evidence of cardiac disease in this group dopamine did not produce an ischemic depression of the S-T segment At high dosages a junctional depression of the S-T segment and an increase in the voltage of T and U waves were observed almost constantly

The second group consisted of 62 subjects with typical angina pectoris The exercise test caused ischemic depression of the S-T segment in 61 2 per cent of the cases while dopamine had the same effect in 72 6 per cent of the cases The third group consisted of 45 patients with atypical precordial pain The exercise test was positive in 20 0 per cent of the cases while the dopamine test was positive in 28 9 per cent

During the infusion of dopamine atrial ectopic beats were rarely observed in control subjects in other subjects ventricular ectopic beats were observed in five cases in one case a bigeminy appeared for a short time The test is harmless with little subjective discomfort Anginal pains were not more frequent with the dopamine test than with the exercise test

An interesting observation is that the ischemic ECG signs frequently appeared after the end of the dopamine infusion This might be due to the fact that dopamine induces ischemic effects after a certain latency An alternative hypothesis is its action on ionic exchanges which might hide the ischemic effects on the ECG This is suggested by the results in other patients who at rest showed ischemic changes of the ECG In these cases dopamine frequently caused surprising temporary changes in the shape of the ST segment and T wave toward an almost normal morphology These changes usually appear before the accentuation of basal ischemic damage (Fig 1)

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Letters to the Editor

Pacemaker catheter displacement

To the Editor

The recent report by Dr Preston on Electrocardiographic diagnosis of pacemaker catheter displacement in the JOURNAL (AM HEART J 85 445 1973) provides a simple way of such detection However as can be seen from Figs 2 and 4 of the article the stimulus artifact is not the *only* thing that changes direction the marked left axis deviation of the QRS in Fig 2 is no longer evident in Fig 4 (the precordial leads are also different) It would be of interest to know how many of Dr Preston s patients with catheter displacement showed a significant change in QRS and how many with stimulus artifact change showed a change in QRS

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Reply

To the Editor

Dr Klein correctly points out that the mean QRS vector also changed in the one case for which full electrocardiograms were shown Also in Case 3 (Table I) the catheter displacement produced a clear change in the QRS vector and in Cases 5 and 7 the displacement was into the right atrium with subsequent loss of ventricular pacing

I agree with Dr Klein s inference that catheter displacement can be diagnosed by changes in the QRS configuration as well as changes in the pacer artifact vector When the catheter is displaced to outside of the right ventricle however there is no pacer induced QRS with which to make a comparison and in writing the article I chose not to discuss QRS changes so as to emphasize examination of the pacemaker artifact vector

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Complications of transfemoral coronary arteriography and their prevention using heparin

Coronary arteriography using the percutaneous femoral (Judkins) approach was introduced five years ago but only recently have reports appeared stressing the distressing complication rate. Chahine and colleagues[1] reported a 5 per cent incidence of myocardial infarction, stroke, or sudden death. Takaro and associates[2] reviewed 1,800 procedures from 20 Veterans hospitals and reported a 2.4 per cent fatality rate, attributing the majority of these deaths to thromboemboli.[3] Green and co-workers[3] reported 20 complications in 445 cases. These included five femoral thromboses, one of which was fatal.

In November 1970 those using the five catheterization laboratories in Seattle met informally to share their experience. There were 17 deaths associated with approximately 900 procedures over a three year period. Analysis of the 184 cases from the Providence Heart Center revealed 16 major complications with six deaths. Despite the liberal use of heparinized saline, the high incidence of thromboembolism was apparent. Furthermore, no learning curve was evident, with the complications being evenly spread over three years. At that time I reported eight months' experience using heparin 50 mg. immediately following the arterial puncture and an equal quantity of protamine sulfate at the end of the procedure. Thromboembolic complications stopped *abruptly*. *This initial experience* now extends to nearly three years and over 200 procedures, still without a death or a major or minor thromboembolic complication. Furthermore, there have been no complications as a direct result of using heparin (currently we use 80 to 100 mg.). Nachnani and co-workers[4] described submicroscopic thrombi on polyurethane catheters despite the use of heparin, but if this occurs clinically it is apparently insignificant.

Experience at three Seattle hospitals (Providence, Swedish, and Virginia Mason) now includes over 1,000 coronary arteriograms using total heparinization without fatality or thromboembolic complication.

The Seattle experience demonstrates the safety and efficacy of a single large dose of heparin before left ventriculography and selective coronary arteriography by way of the transfemoral approach and suggests that this method be employed until non-thrombogenic catheters and guide wires become available.

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Editorial

Central venous pressure Physiological significance and clinical implications*

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With the recent advent of continuous *patient monitoring* a factor frequently recorded is the central venous pressure There is little doubt that knowing the level of central venous pressure and its changes can be of life saving value in some situations such as in the immediate post operative period following some types of cardiac surgery On the other hand central venous pressure measurements have been extended to other clinical situations without as much reason and occasionally are used as a *routine procedure in intensive care* units or in monitoring programs This has expanded considerably with the development of bedside catheterization techniques The goal of the present editorial therefore is to bring into focus the physiological significance of central venous pressure its value as a clinical measurement and the relative advisability of making central venous pressure measurements in view of potential hazards particularly when made as a *routine procedure*

When one speaks of central venous pressure he ideally means the pressure in the right atrium However the pressure in the large systemic veins inside the chest of a supine person is almost invariably within 1 mm Hg of the pressure in the right atrium because the negative pressure of the thorax keeps these large veins in a distended state so that resistance to blood flow from them to the right atrium is extremely slight[1-3] Therefore central venous pressure can normally be measured with accuracy when the tip of the catheter is placed either into any of the great systemic veins of the thorax or into the right atrium itself

Physiological significance of central venous pressure

Right atrial pressure (central venous pressure) has two major physiological effects First it is this pressure that promotes filling of the heart during diastole and thereby plays a major role in determining the amount of blood pumped by the heart each minute—that is the level of cardiac output[4-7] For instance a 1 mm Hg increase in right atrial pressure can at times increase the cardiac output as much as 50 per cent and *several mm Hg increase* can cause as much as a threefold increase in cardiac output Therefore it is immediately obvious that even slight changes in central venous pressure are significant in the control of over all circulatory adequacy

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Book reviews

√CARDIOVASCULAR CLINICS vol 4 No 3 Pediatric Cardiology Mary Allen Engle M D Guest editor Philadelphia 1972 F A Davis Company 366 pp Price $12 00

This volume of Cardiovascular Clinics on Pediatric Cardiology is another excellent practical publication Mary Allen Engle has rendered an excellent service to cardiology She has gathered subjects of importance written by capable contributors The book is written not only for the pediatric cardiologist but for all physicians who treat heart disease in children The many subjects discussed are well selected and clearly presented This is another excellent addition to the series on Cardiovascular Clinics Dr Engle has done a fine job

√VECTORCARDIOGRAPHY By Alberto Benchimol M D Baltimore 1973 The Williams & Wilkins Company 223 pp Price $18 50

Benchimol s book on vectorcardiography briefly reviews the principle of vectorcardiography lead systems and its application in clinical medicine. The selected systems discussed and the Frank system generally used are not clinically practical nor do any of them correct as is so often claimed the many variables that influence the resultant recording in all people or in the same person at all times The Frank system is difficult to apply in infants very sick patients and patients with chest deformities as well as difficult to repeat precise electrode placements at all times Until a simple practical method is introduced for general use such as the tetrahedral system vectorcardiography will never succeed as well as electrocardiography in clinical cardiology This book does present the VCG manifestations in selected common cardiac illnesses very well and is a useful book for beginners The field of course is much more extensive Therefore to become an expert in this field a study of the medical literature and a great deal of experience are necessary This book is a good one and is written for clinical application

Announcements

Pan Pacific Surgical Association Congress

The Pan Pacific Surgical Association announces its Thirteenth Congress to be held February 15 through 21 1975 in Honolulu Hawaii The Congress will convene at the Hilton Hawaiian Village Hotel and concurrent meetings will be held in anesthesiology colon and anorectal surgery general surgery neurosurgery obstetrics and gynecology ophthalmology orthopedic surgery otolaryngology plastic surgery thoracic cardiovascular surgery and urology

For further details regarding the Congress please write Dr Cesar B DeJesus Pan Pacific Surgical Association 236 Alexander Young Building Honolulu Hawaii 96813

1973 Pediatric Cardiology Examination

The next examination in Pediatric Cardiology will be given in the fall of 1973 in the following manner

The written examination will be given on October 2 1973 in four cities Atlanta Chicago Philadelphia and San Francisco This part of the examination will require a full day A subsequent oral examination will be held on October 18 and 19 1973 in Chicago Illinois

Several rules regarding these examinations require emphasis (1) The fee paid for the examination is valid for the 1973 examination only (2) In order to be eligible to take the oral portion of the examination the candidate will have to achieve a *qualifying* score on the written examination (Please note that a *qualifying* grade is not necessarily a *passing* grade It would be possible to qualify with a low passing grade on the written pass the oral and still average out to a failing *total* score Conversely it would be possible to score high enough on the oral portion to pull a low qualifying written grade up to a total passing level) (3) A qualifying score on the 1973 written portion is valid only for the 1973 oral portion Any candidate who does not take the 1973 oral portion or who does not achieve a total passing grade in 1973 must take the entire examination on any subsequent attempt (4) Candidates who do not qualify on the written examination or who do not pass the total examination must pay a new examination fee for any subsequent re examination

After the fall of 1973 examination subsequent examinations will be administered every other year—i e 1975 1977 1979 etc Since there will be a two year hiatus between the 1973 and 1975 examinations the deadline for receipt of applications for the 1973 examination was extended until July 1 1973

Still another modifier of the principle that a damaged heart is associated with increased central venous pressure is the effect of neural stimulation on the heart. Even without neural stimulation the heart has the capacity to pump two to three times normal amounts of cardiac output without significant elevation of the central venous pressure.[4,5] Therefore, slight damage to the heart rarely causes a noticeable change in central venous pressure. And even when cardiac damage becomes moderately extensive, the central venous pressure is still likely to remain within normal limits because of the compensating effects of neural stimulation. For instance, the fast heart rate and sometimes increased thrust of the heart in moderate heart disease are both manifestations of increased neural drive to the heart initiated by reflexes (1) from the heart itself,[21] (2) from baroreceptors in the great arteries,[22,23] or occasionally (3) from chemosensitive areas in the brain.[24] Thus, the increased neural drive to the heart can often compensate for diminished intrinsic cardiac performance, and the result is often an insignificant change or no change in central venous pressure despite moderately severe cardiac debility.

Effect of tendency for venous return on central venous pressure. One can readily understand that when increased quantities of blood are attempting to return to the heart from the peripheral circulation, this also will increase the central venous pressure. However, if the heart is completely normal, even doubling the venous return will cause only a 1 to 2 mm. Hg increase in central venous pressure because the heart will simply pump the increased blood flowing into the right atrium.[25] Therefore, in the face of a normal heart, the tendency for venous return must increase vastly to raise central venous pressure significantly.

On the other hand, if the pumping effectiveness of the heart has been severely diminished, even the slightest increased tendency for venous return may engorge the central veins and the right atrium with so much blood that the central venous pressure will rise markedly. This is the effect that occurs in chronic congestive heart failure in which the heart itself is weak in addition to the greatly increased tendency for venous return, thus markedly elevating central venous pressure.

Causes of increased tendency for venous return. Two principal causes of increased tendency for venous return are (1) decreased resistance to blood flow from the arteries to the veins[2,26,27] and (2) increased ratio of blood volume to vascular blood holding capacity.[2,28]

An ultimate form of decreased peripheral resistance occurs in patients with large A-V fistulae, in which case the tendency for venous return can often be increased, even chronically, to as much as two to three times normal.[29,30] Yet here again, if the heart has sufficient pumping effectiveness, the excess blood returning to the heart will be pumped immediately on into the arteries so that the increase in central venous pressure may be as little as 1 mm. Hg.

An increase in the ratio of blood volume to vascular blood holding capacity means simply that more blood is present in the vascular tree than the vascular tree is designed to hold. For instance, let us assume that the blood volume is increased 50 per cent but that the vascular tree is still of normal basic size. To accommodate the increased volume, all or most of the blood vessels of the body become considerably distended. As a result, the pressures in all these vessels increase, and these increased pressures increase the tendency for blood to flow from the peripheral vessels toward the low pressure area of the central veins.[28] The greater the pressure differences between the peripheral vessels and the central veins, the greater also will be the rate of venous return. Yet if the heart has normal pumping effectiveness, it is very difficult for the venous return to rise high enough to cause more than minor increases in central venous pressure. Yet, on the other hand, the combination of a weakened heart and greatly increased blood volume can cause inordinately elevated central venous pressure.

Effect of external cardiac pressure on central venous pressure. Since the manometers used for measuring central venous pressure are themselves exposed to atmospheric pressure, any change in pressure surrounding the heart and central veins will be reflected by a similar change in the pressure reading from the manometer. A classic example of this effect occurs in cardiac

The second reason for extreme significance of central venous pressure is that it acts as a back pressure on the systemic circulation to oppose return of blood from the peripheral blood vessels into the heart [2,8] Here again, relatively slight changes in central venous pressure can under some conditions have marked effects on the circulation For instance, *in an animal whose cardiovascular reflexes have been blocked* an increase in central venous pressure from its normal value of approximately 0 mm Hg to a positive value of only 7 mm Hg will usually completely stop venous return

Fortunately the extreme effects on both the heart and on venous return caused by changes in central venous pressure are greatly moderated by the circulatory neural reflexes [8,11] Therefore, under normal conditions the central venous pressure can change upward or downward several mm Hg without significantly altering blood flow in the circulatory periphery And by the same token this means that measurements of the central venous pressure in the normal person can vary as much as 3 to 4 mm Hg without having real significance Yet there are limits to function of the neural reflexes, so that central venous pressure changes beyond a few mm Hg do have serious effects on function of the circulation

Normal and abnormal factors that alter central venous pressure

Two very obvious factors that affect central venous pressure are (1) pumping effectiveness of the heart and (2) tendency for venous return However another factor that can alter central venous pressure tremendously and that is often forgotten is (3) the pressure surrounding the heart These three different factors affect central venous pressures in different ways and they all have different physiological significances as follows

Role of the heart in determining central venous pressure One can readily understand that decreased effectiveness of the heart as a pump will tend to dam blood behind the heart *and, therefore* will tend to elevate central venous pressure [12,15] However this simple viewpoint needs to be modified in several different ways

First cardiac damage is not always associated with elevated central venous pressure For instance acute damage to the left ventricle alone without significant damage to the right ventricle occasionally causes either no change in right atrial pressure or even a decrease [12,14] The reason for this is that the associated pulmonary congestion causes large *amounts of blood to* translocate from the systemic circulation into the lungs When this happens, too little blood is available in the systemic circulation for adequate return of blood through the systemic veins into the right atrium Yet, at the same time *the right heart* is still pumping blood with almost usual effectiveness. Therefore in the face of an almost normal right heart but too little return of blood to the heart, one can readily understand why acute left ventricular failure is frequently associated with very little change in central venous pressure, sometimes with a slight rise sometimes with no change at all and occasionally with an actual decrease

A second modification of the principle that a damaged heart causes increased central venous pressure is that chronic cardiac damage almost always increases the central venous pressure far more than does acute damage [12,14,16] For instance acute generalized damage of the heart that reduces the cardiac output almost to lethal levels is often associated with no more than a few mm Hg rise in central venous pressure Yet as the condition proceeds into a chronic state the central venous pressure may rise as much as 15 to 20 mm Hg This chronic effect is generally caused by renal fluid retention secondary to the cardiac debility with subsequent increase in blood volume Initiating causes of the fluid retention are (1) slightly reduced arterial pressure which causes reduction in renal blood flow and glomerular filtration [17,18] (2) an intense increase in sympathetic vasoconstriction of the renal arterioles which further reduces glomerular filtration and (3) an increased secretion of aldosterone which in turn promotes salt and water retention by the kidneys [19,20] Therefore in chronic cardiac insufficiency the increased central venous pressure is a product not only of reduced pumping effectiveness of the heart but also of increased tendency for venous return caused by excess body fluid and blood [illegible]

Still another modifier of the principle that a damaged heart is associated with increased central venous pressure is the effect of neural stimulation on the heart. Even without neural stimulation the heart has the capacity to pump two to three times normal amounts of cardiac output without significant elevation of the central venous pressure.[4,6] Therefore slight damage to the heart rarely causes a noticeable change in central venous pressure. And even when cardiac damage becomes moderately extensive the central venous pressure is still likely to remain within normal limits because of the compensating effects of neural stimulation. For instance the fast heart rate and sometimes increased thrust of the heart in moderate heart disease are both manifestations of increased neural drive to the heart initiated by reflexes (1) from the heart itself,[21] (2) from baroreceptors in the great arteries,[22,23] or occasionally (3) from chemosensitive areas in the brain.[4] Thus the increased neural drive to the heart can often compensate for diminished intrinsic cardiac performance and the result is often an insignificant change or no change in central venous pressure despite moderately severe cardiac debility.

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tamponade in which the pressure within the pericardial cavity is greatly increased This increased pressure makes it impossible for the right atrium to fill with blood until the central venous pressure outside the pericardium rises to a level slightly above the pericardial pressure [31,32] Yet, when the right atrium does fill adequately with blood, the blood can be pumped as usual by the heart Therefore, even if the heart itself is normal, the central venous pressure will be increased an amount almost equal to the cardiac tamponade pressure If in addition to the cardiac tamponade the pumping effectiveness of the heart is also reduced, this can cause still more rise in central venous pressure

Though cardiac tamponade is a dramatic example of the effect of external cardiac pressure on central venous pressure, a much more common example is simply pressure changes related to respiration With each breathing cycle the pressure surrounding the heart and great veins of the chest increases and decreases Therefore the measured central venous pressure also rises and falls [33,34] In addition, respiratory abnormalities can often cause chronic elevation or depression of venous pressure for instance

1 If a patient develops bilateral pneumothorax or if the thorax is opened the pericardial pressure can rise from its normal value of −4 mm Hg up to a value approaching atmospheric pressure, thus elevating the central venous pressure by approximately the same amount [10]

2 Positive pressure breathing by a patient increases the external cardiac pressure sometimes to many mm Hg positive pressure and, therefore, can also elevate the central venous pressure [35]

3 Increased resistance to airflow in the lungs, such as in asthma or in some instances of emphysema can often cause greatly increased positive intra alveolar pressures during expiration, thereby seriously increasing the average external cardiac pressure this pressure rise is also reflected in the central venous pressure [33]

4 When patients overexpand their lungs, the increased stretch of the lungs increases the recoil pressure of the lungs, which in turn *decreases* the pressure surrounding the heart and results in a corresponding decrease in central venous pressure Therefore, simply changing the average volume of air in the lungs will significantly alter the central venous pressure

In summary, external cardiac factors related either to the pericardium, as in cardiac tamponade, or to positive or negative pressures caused by normal or abnormal respiration can frequently alter the central venous pressure as much as 4 to 5 mm Hg and occasionally as much as 20 to 30 mm Hg Since this variable is not always directly related to the adequacy of the circulation itself, it can often obscure the cardiac or peripheral circulatory factors that tend to alter the central venous pressure

Hydrostatic pressure reference level for measuring central venous pressure

Another problem in assessing the significance of central venous pressure measurements is the hydrostatic pressure level to which the central venous pressure is referred It has already been pointed out that even a millimeter or so pressure change can sometimes cause as much as 50 to 100 per cent change in cardiac output If one wishes to assess the adequacy of input pressure to the heart it is important that the pressure level within the right atrium be estimated accurately within 1 mm Hg Therefore, what is the proper hydrostatic pressure level to which the central venous pressure should be referred? One of the most widely used reference levels is that of Winsor and Burch[36] based on measurements in a large number of adults They found the pressure to vary least from one normal supine person to another when the hydrostatic reference level was considered to be approximately the level of the posterior surface of the right atrium In other hemodynamic studies in dogs, Guyton and Greganti[37] showed that the right atrial pressure remains almost exactly constant in an animal rotated into any position in space provided that the hydrostatic reference point is the geometric center of the tricuspid valve This point was found to be 61 per cent of the thickness of the chest in front of the animal s back and 77 per cent of the distance from the suprasternal notch to the tip of the xiphoid process

Yet, regardless of the precise hydrostatic

reference point used by each investigator or clinician it is very clear that the absolute value of the central venous pressure measurement is no more accurate than the precision of the hydrostatic reference level to which the pressure is referred On the other hand if one is looking simply for *changes* in central venous pressure in a single patient the hydrostatic reference level becomes of little importance

Clinical value of central venous pressure measurements

The discussion thus far has presented two contrasting points of view first the extreme importance of central venous pressure in determining both cardiac output and venous return but second the many different factors that can alter the central venous pressure and thereby often make difficult the interpretation of central venous pressure measurements The extreme importance of central venous pressure explains the desire of many clinicians to measure it or even to monitor it continuously Yet on the other hand the difficulty of deciding which of the many determinants of central venous pressure might be causing an abnormal pressure mitigates against the usefulness of the measurements that are made When one is almost certain which of the multiple factors is likely to alter the central venous pressure a continuous record of the pressure is often very valuable for alerting one to a changing condition For instance following acute cardiac surgery it is usually the heart that is the determining factor of changes in central venous pressure or it might be a combination of the heart and the blood volume if significant quantities of parenteral fluid are being administered But at least the choices are few

Another instance in which central venous pressure measurements seem to have been used to advantage is in the treatment of circulatory shock particularly when the treatment involves administration of large volumes of fluid For instance studies by Brand and associates[38] and others have indicated the importance of keeping a slightly elevated central venous pressure during the course of fluid administration in severe degrees of circulatory shock The slightly elevated central venous pressure can be particularly helpful in making the heart pump a normal cardiac output even when the cardiac strength has become decreased as occurs in the late stages of circulatory shock[39,40]

But now we come to the less acute and less life threatening situations in which one might wish to know the central venous pressure level but in which this is not a necessary component either of diagnosis or of therapy For instance does one need to know the central venous pressure to diagnose congestive heart failure? In general he can estimate this within 1 to 2 mm Hg by measuring the peripheral venous pressure because the veins in severe congestive failure are so well distended that there is little pressure drop from the peripheral veins to the heart Indeed a good clinician can estimate the central venous pressure within 2 to 3 mm Hg by simply observing the degree of distention of the neck veins in both the supine and sitting positions And such clinical signs as skin color skin temperature pulse rate cardiac thrust the dyspnea index presence or absence of pulmonary râles and so forth are usually much more directly to the point of the circulatory deficiency than is the central venous pressure anyway

Thus it is with ambivalence that we have discussed central venous pressure in view of the clear and unmistakable importance of this pressure level to the function of the circulatory system but also in view of the difficulty of interpretation and the possible hazards of the procedure itself These hazards are generally well known but they are sufficiently important that they should be left in the mind of the reader (1) possible clotting aftermaths (2) possible internal damage to the blood vessels themselves or to the heart (3) possible introduction of infection into the circulation and (4) inadvertent initiation of cardiac arrhythmias—sometimes even cardiac fibrillation particularly when a catheter inadvertently passes into the right ventricle or when an electrical current is carried to the inner wall of the heart from the recording manometer through the catheter a not too uncommon cause of death

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Fig 1 A and B The opacified left ventricle in end diastole (A left) and in end systole (B right) before operation

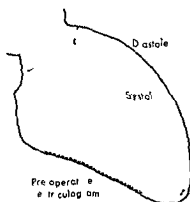


Fig 1C Superimposed tracings of the outline in both phase illustrate akinesis of the inferior wall and hypokinesis of the anterior and apical segments of the left ventricle

Table I Type and site of instances of wall asynergy The site refers to left ventricular areas visualized on ventriculograms obtained in the right oblique position

Type	*Site of asynergy*		
	Anterior	*Apex*	*Inferior*
Akinesis	2	4	9
Hypokinesis	12	19	2

and true aneurysm were not included in this series The walls of the left ventricle identified as anterior apical and inferior were studied separately although most patients had more than one asynergic wall involvement or instances of asynergy Only asynergic walls associated with patent grafts to corresponding coronary arteries were included in the study Forty eight such instances of ventricular wall asynergy were found in 37 patients and are described in Table I

A standard twelve lead ECG was recorded on a direct writing Sanborn machine The technique of recording VCG s was that devised by Frank using the fifth intercostal space with the patient in the sitting position The recordings were done on a 1507A Vector Programmer (Hewlett Packard) The ECG and VCG were recorded on the same day Criteria used for the diagnosis of transmural infarction by ECG and VCG were those which have been generally accepted [11-20]

The distribution of asynergy and myocardial infarction (MI) as diagnosed by ECG VCG excluding left ventricular hypertrophy (LVH) and left bundle branch block (LBBB) are shown in Table II Infarctions were detected in the following areas anterior anterolateral high lateral anteroseptal *inferior* and *true posterior* and thus were studied separately There were 23 instances of infarction diagnosed by ECG *criteria* and 24 instances detected by VCG criteria Nine instances of infarction were excluded because they were not related to areas supplied by coronary arteries having patent grafts Infarctions localized to the anterior anterolateral high lateral and anteroseptal areas were related to

Clinical communications

Improvement of left ventricular asynergy following aortocoronary bypass surgery related to preoperative electrocardiogram and vectorcardiogram

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In the last three years an increasing number of patients have had aorta to coronary saphenous bypass grafts.[1-6] Studies from this Institution[7,8] have shown that localized disorder of left ventricular (LV) wall contraction or asynergy may be partially or totally corrected following this type of operation. The present study was undertaken to determine whether the electrocardiogram and vectorcardiogram (ECG-VCG) might predict the outcome of these anomalies of contraction postoperatively.

Materials and methods

Anomalies of ventricular contraction localized to the anterior, apex, and inferior areas of the left ventricle were studied separately. These anomalies of contraction were detected among 50 patients who were from the first group operated upon in this Institution. We have excluded subjects who had internal mammary artery implantation or muscle resection in addition to the bypass graft procedures. All these patients had complete pre-operative studies, namely ECG, VCG, coronary arteriography, and left ventriculography. Of these 13 patients had normal preoperative ventriculograms and were not part of this study. From the remaining 37, 32 were men and 5 women; their ages ranged from 36 to 65 years, the mean for both men and women being 50 years.

Selective coronary arteriography and bypass graft opacification were obtained with preshaped polyethylene catheters introduced by a percutaneous transfemoral route, a method described previously.[9] Cineventriculography was also performed through a retrograde percutaneous femoral approach.

The left ventricle was considered normal when synchronous concentric and uniform contraction of all its segments could be demonstrated. In contrast to the classification of other investigators,[10] we have limited the term asynergy to the following two abnormalities of contraction: (1) akinesia indicating absence of wall movement and (2) hypokinesis indicating incomplete wall movement.

Cases showing paradoxical movement

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Table V Outcome of LV asynergy after operation

Asynergy	ECG–VCG												Total no
	Inferior wall			Anterior wall			Apex			All sites			
	U*	I	N	U	I	N	U	I	N	U	I	N	
Hypokinesis													
Without infarction pattern	0	0	2	2	1	4	3	2	9	5	3	15	23
With infarction pattern	0	0	0	3	1	1	2	3	0	5	4	1	10
Akinesis													
Without infarction pattern	2	0	0	0	0	0	0	0	0	2	0	0	2
With infarction pattern	7	0	0	2	0	0	4	0	0	13	0	0	13

*U U hang d I mp o ed N r t rn t normal cont act n.

whereas hypokinesis with infarction improved completely in only one of 10 cases ($p < 0.01$) The site of asynergy whether anterior or apical did not matter Of the anterior wall hypokinesis seven of 12 instances improved (58 3 per cent) whereas 14 of 19 cases of apical hypokinesis also showed a better contraction (73 6 per cent) Only two instances of inferior wall hypokinesis were observed and both returned to normal contraction Figs 1 and 2 illustrate the fate of left ventricular asynergy in a ca e of inferior wall akinesis and hypokinesis of the anterior and apical segments The inferior wall akinesis persisted after operation in this patient with an inferior wall infarction whereas the contraction of the anterior and apical segments returned to normal As shown in Table III no relationship between ischemic changes identified by horizontal or sagging ST depression with or without negative T wave and outcome of left ventricular wall asynergy could be observed since such alterations were rarely found without evidence of infarction

The following observations may be stressed (1) hypokinesis improved frequently whereas akinesis remained unchanged (2) hypokinesis without evidence of old myocardial infarction was frequently completely corrected following operation whereas hypokinetic areas associated with an old myocardial infarction seldom return to normal contraction

Discussion

Left ventricular asynergy may be due to scar tissue of previous myocardial infarction or to myocardial ischemia From our observations it appears that akinesis is most frequently related to an extensive myocardial infarction and hence almost always irreversible The only two instance of akinesis without evidence of infarction were located at the inferior wall where it may have been undetected because of the known limitation of these techniques in the diagnosis of infarction in that particular area Akinesis observed in this series never improved in spite of correction of the circulatory deficit by aorta to-coronary bypass graft and was most likely due to noncontractile scar tissue of previous infarction

Hypokinesis however may or may not be associated with myocardial infarction The improvement following this type of surgery of most hypokinetic walls without evidence of previous myocardial infarction indicates that a circulatory deficit was responsible and that these asynergic walls contained viable ischemic muscle which may contract better after operation The lack of improvement may be explained in three of the five instances of hypokinesis without infarction Unimproved hypokinesis of the anterior and apical walls was observed in a patient with an aorta to anterior descending graft which had a stenosis reducing its lumen by 50 per cent possibly responsible for persisting ischemic

Table II. Site of asynergy and of myocardial infarction as diagnosed by ECG VCG (excluding LVH and LBBB)

Site of asynergy	Site of MI					
	Anterior	*Anterolateral*	*High lateral*	*Anteroseptal*	*Inferior*	*True posterior*
ECG						
Anterior	—	2	—	3	—	—
Apex	—	3	—	7	—	—
Inferior	—	—	—	—	7	1
VCG						
Anterior	—	2	—	4	—	—
Apex	—	3	—	7	—	—
Inferior	—	—	—	—	7	1

Table III. Distribution of asynergy and ECG findings (excluding MI, LVH, and LBBB)

Site of asynergy	ECG abnormalities		
	Ischemic changes	*Nonspecific ST-T changes*	*Normal ECG*
Anterior	–	3	3
Apex	3	5	7
Inferior	1	1	2

Table IV. Correlation between ECG evidence of old MI and type of asynergy with respect to the site of asynergy and localization of ECG abnormalities

ECG VCG evidence of infarction	No.	Type	
		Akinesis	*Hypokinesis*
Inferior and true posterior	7	7	0
Anterior* wall and/or apex	16	6	10

*Including anterolateral, high lateral, and anteroseptal.

lesions of the left main trunk, left anterior descending, and its first diagonal branch or left circumflex artery. Infarctions of the inferior and true posterior areas were related to lesions of the right coronary artery (if right coronary dominant) or left circumflex (if left circumflex dominant).

Table III relates the distribution of asynergy and ECG findings other than MI and excluding LVH and LBBB.

All investigational procedures mentioned above were performed between two and three weeks prior to operation and repeated about three weeks following the operation.

Results

A good correlation exists between ECG evidence of old MI and abnormal ventricular contraction with respect to the site of asynergy on the ventriculogram and localization of the infarction pattern by ECG VCG (Table IV).

As shown in Table V, the outcome of asynergy of ventricular walls, inferior, anterior, and apical, is described for hypokinesis and akinesis in both conditions with and without ECG evidence of old myocardial infarction. It may be noted that 23 of the 33 instances of hypokinesis (70 per cent) improved, whereas akinesis remained unchanged. Furthermore, 18 of 23 instances of hypokinesis without ECG evidence of infarction improved (78.2 per cent), whereas only five of 10 instances of hypokinesis with infarction showed a similar favorable outcome (p = N.S.). It is also of interest to note that 15 of the 23 cases of hypokinesis without ECG pattern of infarction returned to normal contraction (65 per cent).

whereas evidence of an old myocardial in farction may predict a partial improve ment only

Summary

The preoperative ECG s and VCG s of 37 patients were studied to determine whether these techniques might help to forecast the outcome of left ventricular asynergy following aortocoronary saphe nous vein graft surgery It was found that akinesis was always associated with a pat tern of old myocardial infarction and that it always remained unchanged after opera tion Hypokinesis however was frequently improved The incidence and degree of improvement were somewhat related to the presence or absence of old myocardial in farction Hypokinesis without myocardial infarction improved slightly more fre quently than that associated with a myo cardial infarction (78 2 vs 50 per cent) However 65 per cent of the cases of hypo kinesis without myocardial infarction re turned to normal contraction following operation whereas only 10 per cent of the cases with hypokinesis and myocardial in farction were completely improved These findings suggest that the preoperative ECG and VCG may reasonably predict the out come of hypokinesis following aortocoro nary bypass surgery but only in terms of complete recovery which is most frequently observed in hypokinesis without ECG evi dence of old myocardial infarction

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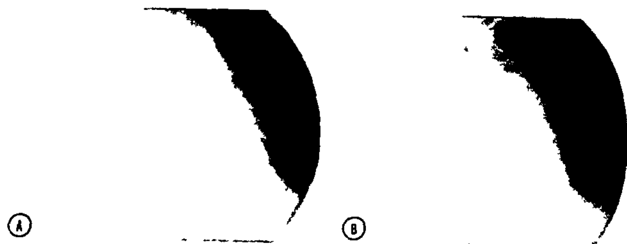


Fig 2 *A* and *B* The opacified left ventricle in end diastole (*A* left) and in end systole (*B* right) after operation

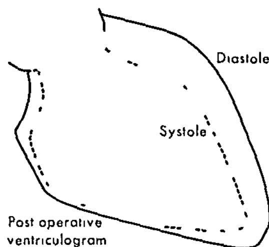


Fig 2C Comparison of these images shows a return to normal contraction of the anterior and apical segments but a persisting akinesis of the inferior wall

changes In another patient with unimproved hypokinesis of the anterior and apical segments, ECG changes during the early postoperative course suggested an anterior wall infarction As for the only instance which remained unexplained one may assume that chronic ischemia of long standing may have produced irreversible muscle changes other than a circumscribed myocardial infarction or that the myocardial infarction was not detected The partial improvement of the three instances of hypokinesis without infarction may be explained on the same basis

On the other hand, hypokinesis associated with an ECG pattern of old myocardial infarction seldom returns to normal contraction in spite of an apparent adequate correction of the circulatory deficit suggesting that scar tissue is the most significant factor In fact, only one such case showed a return to normal contraction It should be noted, however that the infarction was evident only on the VCG, suggesting a small area of fibrosis which may not have altered the ventricular contraction pattern as observed at ventriculography In cases where a partial recovery was observed it is likely that previously ischemic but viable muscle intermingled with or surrounding fibrous tissue became better perfused following operation and hence showed a better contraction

Our study confirms the reports of others which have indicated a fairly good correlation between zones of altered ventricular contraction and sites of coronary artery narrowing [21] It has also demonstrated that infarctions as documented by ECG and VCG are appropriately located in relation to ventricular zones of asynergy

Our results suggest that the preoperative ECG VCG in patients may predict the outcome of left ventricular contraction following aortocoronary bypass grafts only to a limited degree First the presence or absence of ECG evidence of an old myocardial infarction is the only helpful criterion Second this criterion may be helpful particularly in predicting the outcome of hypokinesis In fact akinesis rarely improves at least in our experience and it is almost invariably associated with an old myocardial infarction As far as hypokinesis is concerned the absence of ECG pattern of an old myocardial infarction may forecast a return to normal contraction



Fig 1 Electrophysiological recordings from Case 1 Shown are Leads V1 I II and III with His bundle electrogram (HBE) Pacing impulses are labeled with arrows His bundle electrogram are labeled *H* The pacing rate is 1?0 per minute and P H interval are li ted and how Wenckebach periodicity The fifth and sixth P waves are blocked proximal to the H potential Paper speed is 100 mm per second and time lines are at 1 second

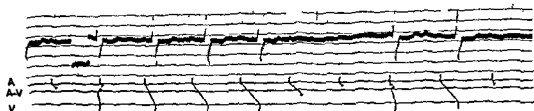


Fig 2 Rhythm strip and ladder diagram showing Wenckebach period terminated with two blocked P waves The upper level of the ladder reflects atrium the middle two levels A V node and the bottom ventricle The third fourth and fifth P waves are conducted with increasing P R intervals The sixth and seventh P waves are blocked A proposed mechanism is presented showing the first P blocked low in the node and the second P blocked at a h gher level (From Langendorf and Pick Circulation 13 381 1956 reproduced with permission of the American Heart Association)

0 10 second and a P R inter al of 0 14 second Incomplete right bundle branch block pattern was also noted

Electrophysiological studies Informed consent was obtained for electrophy iological studies Hi bundle electrograms were recorded with the use of previ ou ly de cr bed techniques [4 7] Atrial pacing was per formed at varied heart rates

The patient was in sinus rhythm at a rate of 60 per minute P H interval was 125 msec P A 20 msec A H 105 msec and HV 40 msec Wenckebach *periods proximal to the His bundle were noted* at a paced rate of 120 per m nute These were generally terminated by one blocked P Se eral atypical cycles were recorded these being terminated by two con secutive P waves blocked proximal to the His bundle (Fig 1)

Comment Langendorf and Pick[2] postu lated that block of two consecutive P waves during a Wenckebach period occurs due to inhomogeneous penetration of the A V node They suggested deeper penetration *of the first impulse and more superficial* penetration of the second impulse (Fig 2) His bundle electrograms in such cases should record block of both P waves prox imal to the His bundle

In the present case His bundle electrograms documented repetitive block prox imal to the His bundle This technique does not allow us to measure the degree of pene tration of the A V node in the two blocked cycles However the results are consistent with Langendorf and Pick s previous hy pothesis

Case 2 A 25 year old man with corrected tetral ogy of Fallot was admitted for cardiac evaluation *ECG* revealed normal inus rhythm at a rate of 70 per minute a P R interval of 0 16 second and a QRS duration of 0 16 second with complete right bundle branch block pattern

E e rophysi logica stuaies The patient was in inus *rhythm at a rate of 65 per minute The con duction intervals were as follows* I H 1?8 msec P A 23 msec A H 105 msec and H V 44 msec *4 3* and 3 2 Wenckebach per ods proximal to H were noted at a paced rate of 150 per minute The Wenckebach periods were typical during 4 3 *con duction* (Fig 3 *A*) With 3 2 A V nodal Wencke bach the following was observed The first P H was *140 msec the second 160 msec and the third P* was blocked proximal to the His bundle The second P was always blocked distal to H (Fig 3 *B*)

Comment In this case 3 2 Wenckebach periods proximal to H were associated with 3 1 A V block Inhomogeneous conduction

Wenckebach periods with repetitive block Evaluation with His bundle recording

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Langendorf[1] in 1948 introduced the term "concealed conduction" to describe the results of partial penetration of an electrical impulse into the A V junction The incompletely penetrating impulse transiently lengthens the A V refractory period modifying the conduction of the subsequent impulse This concept has proved useful in understanding the mechanisms involved in a number of arrhythmias [2-5] Repetitive block of several consecutive atrial impulses can occur when successive impulses partially penetrate the A V conducting system without traversing it completely, producing varying periods of ventricular asystole This phenomenon has been called "repetitive concealed conduction"[2]

Type I second degree A V block (Wenckebach) is characterized by progressive P R prolongation prior to a single dropped beat Termination of a Wenckebach cycle with more than one blocked P wave is rare Langendorf and Pick[2] reported a patient with Wenckebach periods terminated by several blocked atrial impulses and suggested that this was a manifestation of repetitive concealed conduction

In this report we describe two patients with Wenckebach periods and block of two consecutive P waves In one the mechanism appeared similar to that previously postulated by Langendorf and Pick In the second a new mechanism is described In this case long cycle lengths were produced in the His Purkinje system due to A V nodal Wenckebach periods This long cycle prolonged the His Purkinje refractory period in the subsequent cycle so that the second conducted beat of the Wenckebach period (short cycle) was blocked distal to the His bundle This occurred during 3 ? A V nodal Type I block with resulting 3 1 A V block

Both mechanisms can produce unexpected asystole during Type I second degree A V block

Report of cases

Case 1 A 23 year old man was admitted to Cook County Hospital for evaluation of syncope Results of a physical examination were essentially negative Electrocardiogram (ECG) revealed sinus bradycardia at a rate of 53 per minute a QRS duration of

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attributed this to repetitive concealed conduction in the A V junction suggesting that the first blocked sinus impulse had a deeper penetration of the A V node augmenting its refractoriness so that the subsequent sinus impulse could not be transmitted It was postulated that this latter impulse was blocked at a higher level Such inhomogeneous penetration of the A V junction could be responsible for block of multiple atrial impulses

Moe and associates[10] experimentally demonstrated repetitive concealed conduction with as many as six premature atrial impulses blocked in succession Watanabe and Dreifus[11] demonstrated two levels of A V nodal block during 3 1 response in rabbit hearts and suggested inhomogeneous conduction in the A V node Moore[12] employing microelectrode technique in rabbits defined the sites and mechanisms of A V block of serially concealed premature atrial impulses and demonstrated decremental conduction within both the A V node and His Purkinje system

His bundle recording has helped clarify mechanisms of concealed conduction in man permitting accurate localization of sites of conduction delay following blocked premature responses[13,14] This technique was helpful in the present cases In the first patient repetitive block during Wenckebach beating was localized proximal to the His bundle This is in keeping with the postulation of inhomogeneous conduction in the A V node as previously suggested[5]

In the second patient varying depths of penetration were documented with His bundle recording Block of two successive P waves occurred one distal and the other proximal to the His bundle The consecutive blocked P waves did not reflect repetitive concealed conduction Failure of impulse propagation at the A V node (during Type I block) produced long cycle lengths in the His Purkinje system with associated refractory period prolongation This allowed the second beat of the Wenckebach period (short cycle) to be blocked distal to His bundle Thus 3 2 A V nodal Wenckebach periods were associated with 3 1 A V block It should be pointed out that the initiation of this 3 1 block must have occurred with a typical 3 2 Wenckebach period

Clinical implications Although the abnormalities of conduction demonstrated were induced by atrial pacing similar phenomenon could certainly occur during spontaneous beating explaining unexpected blocked P waves during Type I second degree block In patients with bundle branch block long R R cycles could lengthen the refractory period of the functioning bundle branch causing nontransmission during short subsequent cycles 3 1 A V block with bundle branch block could thus represent one of the following (1) 3 1 block proximal to H, (2) 3 1 block distal to H or (3) the mechanism described in Case 2 Mechanism No 2 would appear to be the most serious, suggesting bilateral bundle branch disease[15]

Both types of repetitive block described in this report could produce serious bradyarrhythmias during the course of usually benign Type I second-degree A V block Pharmacologic therapy with atropine or isoproterenol or pacemaker insertion might be necessary

Summary

Two patients are reported in whom repetitive block of two consecutive P waves occurred during Wenckebach beating induced by atrial pacing His bundle recordings revealed block proximal to H in the first case suggesting inhomogeneous conduction in the A V node In the second case long cycle lengths were produced in the His Purkinje system due to A V nodal Wenckebach periods The long cycles prolonged refractory periods in the His Purkinje system so that subsequent beats (short cycles) were blocked distal to H

The repetitive block of consecutive multiple atrial impulses could result in unexpected degrees of ventricular asystole during usually benign Type I second-degree A V block

The authors are grateful to Drs Richard Langendorf and Alfred Pick for their kind permission to use Fig 2 from their previous publication The authors also wish to express their thanks to Mrs Mary Ellen Rosen for the preparation of the illustrations and to Mrs Katherine Evans for the preparation of the manuscript



Fig 3 Wenckebach periods produced with atrial pacing demonstrating block above and below the His bundle The pacing rate is 150 per minute in both panels (*A*) 4 3 Wenckebach periods proximal to the His bundle Note the long H H cycle of 730 msec and the short H H cycle of 435 msec (*B*) 3 2 A V nodal Wenckebach with 3 1 block The second P wave of each cycle is blocked distal to H and the third proximal to H The long H H cycles are 790 msec and the short 435 msec (See text for discussion) Paper speed is 100 mm per second and the time lines are at 1 second

was noted the first P being blocked distal to and the second proximal to the His bundle

The failure of conduction distal to H of the first nonpropagated impulse during 3 1 response was easily explainable It is evident from Fig 3 *B* that H potential occurred at alternating long and short intervals The longer H H cycles were of 790 msec duration while the shorter cycles were 435 msec This long short sequence reflected 3 2 Wenckebach periodicity proximal to H The refractory period of the ventricular specialized conduction system was presumably prolonged in the cycle following the long H H, reflecting the relationship of cycle length and refractory period in the His Purkinje system [8] This prolongation of refractoriness was reflected in block distal to H of the second beat of the Wenckebach sequence (short H H cycle) Since the patient had right bundle branch block block distal to H probably occurred in the left bundle branch

The above interpretation was supported by examining conduction during the 4 3 Wenckebach periods During 4 3 conduction the short H H cycles were 435 msec identical in length to short cycles during 3 2 conduction The long H H cycles were only 730 msec and shorter than the cycles during 3 1 conduction This slight shortening of long H H cycles was of critical degree allowing conduction to occur in the subsequent short cycle

Discussion

In 1925 Lewis and Master[9] demonstrated that a blocked atrial impulse could delay the transmission or completely block a subsequent impulse They also described block of repetitive impulses Langendorf and Pick[2] described block of consecutive impulses during a Wenckebach cycle They

Electrocardiographic findings in single ventricle and related conditions

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Although this subject has been studied for a relatively long time the electrocardiographic features reported by different authors have become more specific as knowledge in the pathology of these malformations has increased[2-6] It is therefore desirable that analysis be based on groups with maximal anatomic and physiological homogeneity Thus two main groups have been established (I and II) with a further three subgroups each (A B and C) (See Table I)

In Group I (Table I) both atrioventricular orifices either independent or fused into a common atrioventricular canal are mainly received by the left ventricle In this group where a total or partial lack of the normal displacement of the atrioventricular canal towards the bulbus cordis appears to be the basic embryologic derangement[4]

Defective displacement of the atrioventricular canal towards the bulbus cordis would be the adequate term Subgroups A B and C concern the extent with which this normal displacement has been lacking

In Subgroup A (Table I) the atrioventricular canal is completely received by the left ventricle The result a bigger left ventricular cavity in comparison with the right ventricle which is reduced to its outflow tract has previously been described as single left ventricle[2] single (primitive) ventricle[5] double inlet left ventricle[4] displaced tricuspid valve[7] etc Common associated malformations with this anomaly are transposition of the great arteries pulmonary stenosis preductal coarctation of the aorta subaortic stenosis etc Less frequent are certain anomalies of the atrioventricular valves including mitral atresia[8,9]

In Subgroup B (Table I) the normal displacement of the atrioventricular canal towards the bulbus cordis although initiated would remain somewhat incomplete Consequently despite a small area of the atrioventricular canal being received by the right ventricle the major portion of this connects with the left ventricular cavity The resulting ventricular proportions although very similar to those in Subgroup A

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completely received by the right ventricle which is greatly enlarged and may appear as a single ventricular chamber The left ventricle deprived from any significant blood filling remains reduced to a very hypoplastic cavity without papillary muscles It is questionable whether these cases are not equivalent to those described as single right ventricle[3] although the finding of the remaining left ventricle has not been quite clear in the latter *Establishing a* parallel with the recent contribution of Liberthson and associates[7] these cases could equally be termed as *displaced mitral* valve[14]

In Subgroup B (Table I) the atrioventricular canal *abnormally displaced towards* the bulbus cordis remains slightly connected to the left ventricle This cavity provided with the posterior group of papillary muscles and accessible to blood filling is of larger size

In Subgroup C (Table I) the exaggerated displacement of the atrioventricular canal towards the bulbus cordis is of lesser degree A comparatively larger area of atrioventricular canal than in Subgroups A and B is received by the left ventricle the cavity of which shelters the two normal groups of papillary muscles and attains a more regular size

Special case In one case with the mitral orifice–ventricular septum relationship fairly similar to the one in Subgroup C and the left ventricle containing only the posterior group of papillary muscles as in Subgroup B we were surprised to find the left ventricle considerably larger than the right *This unusual factor is ascribed to the* hypoplasia of the tricuspid orifice despite part of the mitral orifices being received by the right ventricle the total area of the atrioventricular canal connected to the left ventricle was larger

Material and methods

Of a total of 33 cases studied an exact anatomical diagnosis was obtained in 25 with a fairly reliable diagnostic approach being made in the remainder using all the conventional methods including cardiac catheterization and angiocardiography

The angiocardiographic difference between Group IA IB and IC was based on the presence of the characteristic filling defects (interpreted as papillary muscles) *in the remainder* of the right ventricular cavity Angiocardiographic differentiation between groups IA and IB is not considered feasible

Apart from the basic pertaining subgroup other associations (type of bulboventricular loop[2] pulmonary stenosis and common atrioventricular canal) have been taken into account in analyzing the electrocardiograms of the cases concerned

For general case distribution incidence rates of most frequent associations see Table I

Normal atrial and visceral position was detected in every case A ventricular septal defect was present in all cases in Group I and in all but one case of Subgroup A in Group II

The electrocardiographic criteria used for the diagnosis of atrial and ventricular enlargement have been those proposed by others[15 17]

Results

In grouping the cases for the electrocardiographic analysis the main factors under consideration were the type of bulboventricular loop and the presence or absence of pulmonary outflow obstruction and dextrocardia

I *Group I Subgroups A and B D loop* Subgroups I A and I B have been analyzed together since there were no significant differences among them

A NO PULMONARY STENOSIS Five cases (1 to 5 Table II) There was a sinus rhythm in every case There was a right atrial enlargement in cases 1 to 4 in case 5 biatrial enlargement was diagnosed

The QRS axis (Fig 1) was of almost *+100 degrees in three cases* being of −80 degrees and −10 degrees in cases 3 and 4 respectively A common atrioventricular valve and *normally related great arteries* were found in case 3 Deep Q waves in Leads III and aV_F were absent in all cases Essentially negative complexes *in the* Lead aV_R were found in cases 1 2 4 and 5 Case 3 showed a qR deflection in the right arm lead The initial QRS vector *in the* horizontal plane was directed towards the right anteriorly in all cases (Fig 2)

RS complexes over the entire precordium were noted in cases 1 and 3 ST T digitalis

GROUP I			NORMAL	GROUP II		
A	B	C		C	B	A
RV LV	RV LV	RV LV	R.V. L.V. TPM MPM	R.V. L.V.	RV	R.V.
11	6	2	TOTAL CASES 33 *	1	2	2
D-LOOP 4 L-LOOP 7	D-LOOP 2 L-LOOP 4	D-LOOP 1 L-LOOP 1	B-V LOOP	D-LOOP 1	D-LOOP 2	D-LOOP 2
2A-VV 8 CA-VC 2 MA 1	2A-VV 4 CA-VC 1 MA 1	2A-VV 1 CA-VC 1	A V VALVES	2A-VV 1	CA-VC 2	2A-VV 1 CA-VC 1
4	1	1	PULMONARY ATRESIA&STENOSIS	—	1	—
L 10 R 1	L 6 R —	L 2 R —	CARDIAC APEX	L	L	L

Table I General distribution and classification of our cases The special case the 3 dextrocardia cases and the angiocardiographically proved cases have not been included in this table See text for criteria used to classify the cases RV = right ventricle LV = left ventricle TPM = tricuspid papillary muscle MPM = mitral papillary muscle AVV = atrioventricular valve CAVC = common atrioventricular canal R = right L = left D = dextro L = levo

will vary somewhat from the right ventricular size Effectively the right ventricle receiving a small but definite part of the atrioventricular canal has a true but small sinusal portion with papillary muscles and chordae The cases included in Subgroup B generally come under the same designations as used for those in Subgroup A the associated anomalies being similar Nevertheless, we have established two separate groups to ascertain whether such a small difference in the size of the right ventricle is reflectable in the electrocardiogram

In Subgroup C (Table I) the displacement of the atrioventricular canal towards the bulbus cordis appears nearer to the normal Consequently, a larger area of the atrioventricular canal is received by the right ventricle, the size of which would significantly differ from that in Subgroups A and B The terms of Lambert heart and straddling tricuspid valve [7,10,11] have been used so far to designate malformations with these general characteristics One case with an associated mitral atresia has also been reported in this subgroup [12]

Less common and in turn lesser known are the hearts studied in Group II [2,3,6] As for the atrioventricular canal–ventricular septum relationships the opposite phenomenon characterizing the cases of Group I seems to be the basic feature of the ones in Group II Thus the term Exaggerated displacement of the atrioventricular canal towards the bulbus cordis is indicated for these malformations [13,14]

As in Group I three further subgroups, A B and C have been established in accordance with the extent of this exaggerated displacement In Subgroup A (Table I) the atrioventricular canal common or divided in two atrioventricular orifices, is

completely received by the right ventricle which is greatly enlarged and may appear as a single ventricular chamber The left ventricle deprived from any significant blood filling remains reduced to a very hypoplastic cavity without papillary muscles It is questionable whether these cases are not equivalent to those described as single right ventricle[2] although the finding of the remaining left ventricle has not been quite clear in the latter Establishing a parallel with the recent contribution of Liberthson and associates[3] these cases could equally be termed as displaced mitral valve [14]

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RS complexes over the entire precordium were noted in cases 1 and 3 ST T digitalis

Table II Groups IA and IB—"D" bulboventricular loop—ECG findings

Case No and initials	Sub group	Age	Diagnosis	A V valves	G.A.*	Rhythm
Without P S						
1 R A S	A	1 5 months	N	2	D TGA	S
2 T G P	A	15 days	N	2	D TGA	S
3 R A P	B	1 day/2 months	N	CAVC	Normal	S
4 G G	B	3 months	N	2	D TGA	S
5 J M P	?†	2 years/6 years	A	?	D TGA	S
With P S						
6 M S	A	3 months	N	MA	Normal	AAVC
7 P F	A	3 months	N	CAVC	D TGA	S
8 A G C	?	1 year	A	?	Normal	S

*Abbreviations G A = great arteries N = necropsy A = angiography CAVC = common atrioventricular canal MA = mitral a[illegible] RVH = right ventricular hypertrophy LVH = left ventricular hypertrophy BVH = biventricular hypertrophy P S = pulmonary stenosis
†The angiocardiographic differentiation between group IA and IB and the prediction of the common or divided nature of the A V canal [illegible]

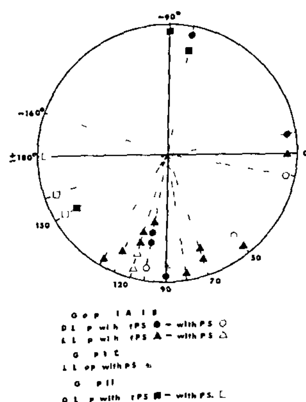


Fig 1 General distribution of the QRS axis in the frontal plane in our cases Cases 22 and 23 are not included because of the undetermined nature of their QRS axis The cases with dextrocardia are excluded from this illustration Note the majority of the cases showing a QRS axis varying between +50 and +130 degrees The three cases with an electrical axis close to −90 degrees having a common atrioventricular valve Nevertheless four other cases with a common atrioventricular orifice had an electrical axis varying from +10 to +180 degrees Note in cases of Group II (with a larger right ventricle) the QRS axis is located more to the right as is also the electrical axis of Group I cases with an L Loop

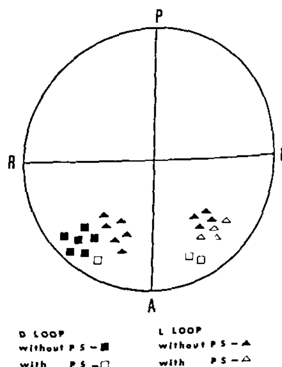


Fig 2 Group I General distribution of the initial QRS forces in the horizontal plane Note the high incidence of abnormally directed initial vectors in the L Loop and pulmonary stenosis cases P = posterior A = anterior R = right L = left

induced changes in the left precordial leads were present in cases 1 3 and 4

Electrocardiographic diagnosis of left ventricular hypertrophy was possible in cases 2 4 and 5 In cases 1 and 3, an electrocardiogram suggesting biventricular hypertrophy was found

B PULMONARY STENOSIS Three cases

Atrial enlargement	Â QRS	Deep-Q III-aVF	aVR	Isodiphasism	ST T changes	Ventricular pattern
RAH	+100°	−	rS	+	+	BVH
RAH	+100	−	rS	−	−	LVH
RAH	−80	−	qR	+	+	BVH
RAH	−10	−	Qr	−	+	LVH
BAH	+90	−	Qr	−	−	LVH
RAH	+50	−	QS	rS	+	LVH
—	+10	−	QS	−	−	LVH
RAH	+100	+	Qr	rS	−	LVH

...sal AAVC = accelerated A V conduction RAH = right atrial hypertrophy LAH = left atrial hypertrophy BAH = biatrial hypertrophy
...en considered to be impossible

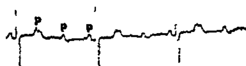


Fig 3 Electrocardiogram of Case 11 Complete heart block recorded in Lead I (age = 4 months)

(6 to 8 Table II) A sinus rhythm was present in all but case 6 where a short PR was found

A right atrial hypertrophy existed in cases 6 and 8 The QRS axis showed a great variability ranging from +10 to +100 degrees (Fig 1) Deep Q waves in Leads III and aV_F were noted in case 8 Essentially negative deflections were seen in Lead aV_R in every case The initial QRS forces in the horizontal plane were abnormally directed towards the left anteriorly in two cases being normal in case 7 (Fig 2)

There was an rS deflection in all precordial leads of cases 6 and 8 and in case 6 ST T changes not induced by digitalis intake existed in the left precordial leads

Left ventricular hypertrophy was diagnosed in every case

II Group I Subgroup A and B L loop

A NO PULMONARY STENOSIS Ten cases (9 to 18 Table III) A sinus rhythm was present in all except case 11 where a complete heart block existed (Fig 3) In cases 9 and 16 (Fig 4) an accelerated atrioventricular conduction was found

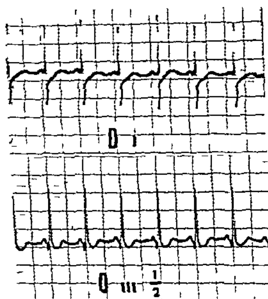


Fig 4 Electrocardiogram of Case 16 Observe the short PR segment without any other alteration in the P and QRS morphologies (accelerated atrioventricular conduction) (age = 3 5 months)

Right atrial enlargement was detected in cases 10 11 12 14 15 and 17 (Fig 5) biatrial hypertrophy being found in case 9 The QRS axis ranged from 0 to +120 degrees (Fig 1) Deep Q waves in Leads III and/or aV_F existed in cases 9 11 14 15 and 18 (Figs 5 and 6) Essentially negative

Table III Groups IA and IB—"L" bulboventricular loop—ECG findings

Case No and initials	Sub group	Age	Diagnosis	A V values	G A	Rhythm
9 V A R	A	2 5 months	N	2	D TGA	AAVC
10 E M L	A	4 5 months	N	2	L TGA	S
11 P P A	A	4 months	N	2	L TGA	CHB*
12 C A	A	2 months	N	CAVC	L TGA	S
13 P V	A	5 months	N	2	L TGA	S
14 L A G	B	4 months	N	2	L TGA	S
15 C P P	B	3 months	N	MA	D TGA	S
16 L Q D	B	3 5 months	N	2	D TGA	AAI
17 L O G	?	12 days/1 month	A	?	L TGA	S
18 S D	?	4 months	A	?	L TGA	S
19 A G	A	1 day	N	2	L TGA	S
20 T N T	B	10 days	N	2	L TGA	S
21 A P F	?	15 months	A	?	L TGA	S

*CHB = complete heart block. For other abbreviations see Table II

Table IV Group IC, ECG findings

Case No and initials	Age	Diagnosis	A V values	G A	Rhythm	Atrial enlargement	A QRS
22 S G	1 month/3 months	N	2	D Malp†	S	RAH	Und
23 A P J	8 months	N	CAVC	D TGA	S	RAH	+90°

*Abbreviations P A = pulmonary atresia Und = undeterminated D Malp = D malposition For other abbreviations see Table II
†A right sided aorta and a left sided pulmonary artery arising both from a right sided morphological right ventricle Both great arteries

deflections in Lead aV_R appeared in each case (Fig 7)

Abnormally directed initial QRS forces in the horizontal plane were noted in cases 9 13 15, and 17 a q wave in Leads V r and V_1 being detected in cases 9 and 13 (Figs 2 and 7) RS morphologies appeared in the entire precordium of cases 10 11 12 13 16, and 17 (Fig 6) Case 15 showed an rS deflection in all precordial leads (Fig 5)

Digitalis induced ST T changes over the left precordial leads were seen in cases 9 10, 12, 13, 15 16 and 18 (Figs 5 6 and 7)

Diagnosis of left ventricular hypertrophy was possible in cases 12 14 15 and 18 (Fig 8), a right ventricular hypertrophy being detected in cases 9 and 11, with bi ventricular enlargement in the remaining cases

B PULMONARY STENOSIS Three cases (19 to 21, Table III) Sinus rhythm signs suggesting right atrial enlargement, a QRS axis almost +110 degrees, and lack of deep Q waves in Leads III and/or aV_F characterized all three cases (Fig 9) Essentially negative morphologies in Lead aV_R existed in 2 cases Initial QRS vectors abnormally directed towards the left anteriorly could be detected in all 3 cases Moreover in case 21, an abnormal q wave was present in Leads V_3r and V_1 RS complexes in the entire precordium (isodiphasism) were found only in case 19 (Fig 9) An rS pattern in the precordial leads was noted in case 20

Digitalis induced ST T changes in the left precordial leads were seen in one case In the remaining two the presence of these same changes could not be attributed to digitalis intake Right ventricular hypertrophy was diagnosed in case 21 with bi ventricular dilatation in case 19 (Fig 9)

III *Group I, Subgroup C D loop*

NO PULMONARY STENOSIS One case (22,

Atrial enlargement	A QRS	Deep-Q III-aV_F	aV_R	Isodiphasism	ST T changes	Ventricular pattern
BAH	+100	+	QS	−	+	RVH
RAH	+80	−	QS	+	+	BVH
RAH	+110	+	Qr	+	−	RVH
RAH	+110	−	QS	+	+	LVH
—	+10	−	QS	+	+	BVH
RAH	0	+	Qr	−	−	LVH
RAH	+115	+	QS	rS	+	LVH
—	+70°	−	QS	+	+	BVH
RAH	+120	−	QS	+	−	BVH
—	+50	+	QS	−	+	LVH
RAH	+110	−	QS	+	+	BVH
RAH	+115	−	Qr	rS	+	—
RAH	+110	−	QR	−	+	RVH

Deep Q III aV_F	aV_R	Isodiphasism	ST T changes	Ventricular pattern	B V loop pulmonary outflow tract
−	QR	+	+	BVH	D Loop—without P S
+	QS	+	−	—	L Loop—with P A *

*Supported by a muscular co s.

Table IV) Briefly the most outstanding features were sinus rhythm right atrial enlargement undetermined QRS axis normal initial QRS forces isodiphasism digitalis induced ST T changes and biventricular hypertrophy Existing QR complex was seen in lead aV_R

IV *Group I Subgroup C I loop*

PULMONARY ATRESIA One case (23 Table IV) The most remarkable electrocardiographic findings of this case were a sinus rhythm right atrial hypertrophy a QRS axis of +90 degrees deep Q waves in Leads III and aV_F a QS complex in Lead aV_R an initial QRS vector abnormally directed towards the left anteriorly and isodiphasism There were no signs of enlargement of any ventricle

V *Group I Subgroup with Dextrocardia L loop*

PULMONARY STENOSIS Three cases (24 to 26 Table V) Sinus rhythm in every case Biatrial enlargement in two cases right atrial hypertrophy being found in the remainder In case 25 the QRS axis was −90 degrees The QRS complex in Lead aV_R was essentially negative in two cases (24 and 26)

Right ventricular hypertrophy was diagnosed in one case Left ventricular enlargement was present in cases 24 and 26

The other electrocardiographic features summarized in Table V are not considered to be of any particular interest

VI *Group II Subgroup A D loop*

TWO CASES (27 and 28 Table VI) The most important electrocardiographic findings in these cases were the presence of an accentuated right ventricular enlargement with initial q waves in the right precordial leads (Fig 10)

VII *Group II Subgroup B D loop*

TWO CASES (29 and 30 Table VI) The QRS axis was of −90 degrees and ±180

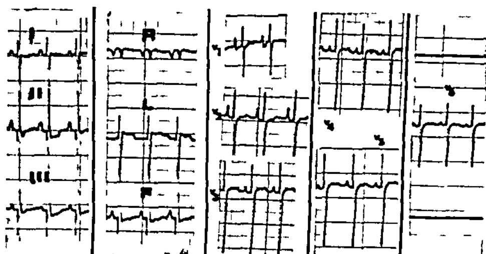


Fig 5 Electrocardiogram of Case 15 The main features are right atrial hypertrophy deep Q waves in Lead III an essentially negative deflection in aV_R ST T changes and rS pattern over the entire precordium (age = 3 months)

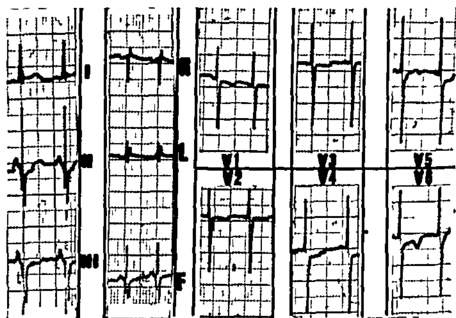


Fig 6 Deep Q waves isodiphasism and ST T changes Electrocardiogram of Case 14 (age = 4 month)

degrees in the two cases respectively both with a common atrioventricular orifice Right atrial and ventricular enlargement were present in both cases

VIII *Group II, Subgroup C, D loop*

ONE CASE (32, Table VI) The most important findings in this case were an undetermined QRS axis and biventricular hypertrophy This latter correlated well with the ventricular proportions of this heart the size of both, left and right ventricle being fairly similar

Special case

This case, the rather unusual anatomic findings of which are displayed above, was a heart in D Loop without pulmonary stenosis and two independent atrioventricular orifices The most important electrocardiographic feature was the existence of biventricular hypertrophy with more conspicuous signs of left ventricular enlargement a factor closely parallel to the anatomic ventricular proportions

Discussion

In accordance with our expectations and as our findings confirmed there are distinct electrocardiographic differences[4,5] between the morphologies of Groups I and II these differences will now be discussed Such clear cut and extreme differ ces as are seen

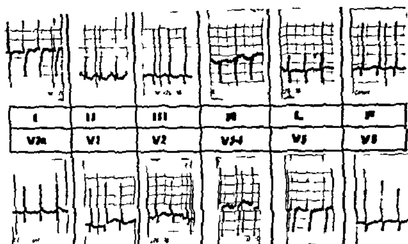


Fig 7 Electrocardiogram of Case 13 The most outstanding findings are the presence of deep Q waves in Lead V_{3R} and V_1 ST T changes and a QS pattern in Lead aV_R (age = 5 months)

in Figs 8 and 10 however are not the general rule in the cases concerned

Right arm morphologies have proved a reliable source of information in establishing the differential diagnosis between Groups I and II when the remaining electrocardiogram does not reveal the obvious differences shown in Figs 8 and 10 Thus essentially downward potentials in Lead aV_R are recorded in 86 9 per cent of our cases in Group I particularly in those pertaining to Subgroups A and B (Tables II III IV and V)[19] On the contrary important upright deflections have been found in most of the cases of Group II (Table VI)

Upon having established and dealt with the major differences between Groups I and II cases the individual findings pertaining to each of these will be treated separately

Group I In good agreement with the anatomic findings a left ventricular enlargement existed in 66 6 per cent of the D loop cases an isolated right ventricular hypertrophy being diagnosed only in L loop cases Similar[4 18] and different[20 21] findings have been reported by others

Biventricular hypertrophy (isodiphasism) found in 34 7 per cent of the material was not related to any particular subgroup The isodiphasism present in 47 8 per cent of our patients and more frequently in L loop cases has already been reported as characteristic in this group of anomalies[19 21 3]

In four L loop cases an unexpected left ventricular enlargement was present It is

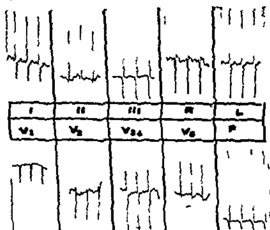


Fig 8 Case 18 Observe the pure left ventricular enlargement with a QS in Lead aV_R and ST T changes in the left precordial leads (age = 4 months)

considered whether an almost anteroposterior relation of the infundibular chamber to the main ventricular cavity combined with unavoidable inexact position of the electrodes might be the origin of such paradoxical findings

An rS pattern in the entire precordium was found in four patients The incidence of this pattern was higher in cases with a D loop and normally related great arteries (as in two of our cases) and has been reported previously[24] In one of the latter cases the height of the r wave increased after the creation of a systemic pulmonary artery anastomosis

Table V Group I—Dextrocardia—ECG findings

Case No and initials	Sub group	Age	Diagnosis	A V valves	G A *	Rhythm	Atrial enlargement
24 J V D	A	8 days	N	2	L TGA	S	RAH
25 F G R	?	2 years	A	?	L TGA	S	BAH
26 P P V	?	8 months/4 years	A	?	L TGA	S	BAH

*See Table II for abbreviations.

Table VI Group II—ECG findings

Case No and initials	Sub group	Age	Diagnosis	A V valves	G A	Rhythm	Atrial enlargement
27 S J	A	4 months	N	CAVC	L TGA	S	LAH
28 I E S	A	19 days	N	2	D TGA	S	—
29 N R	B	15 days	N	CAVC	Normal	S	RAH
30 P F B	B	3 months	N	CAVC	D TGA	S	RAH
31 I A	?	4 months	A	?	D Malp	S	RAH
32 R G D	C	8 days	N	2	D TGA	S	—
33 A G G	S C	1 month	N	2	D Malp	S	BAH

*Abbreviations LP = left posterior LA = left anterior RA = right anterior S C = special case For other abbreviations see Table II and

The essentially negative deflections in Lead aV_R observed in 86 9 per cent of our material and previously by others,[19] seems to be the result of the right ventricular sinus hypoplasia

A right atrial enlargement was present in 73 9 per cent of the cases Biatrial en largement was present in 8 7 per cent all of which presented increased pulmonary blood flow, as previously mentioned [19 21 23 25]

A left atrial hypertrophy has not been found in our material contrary to prior reports [23 26 27]

ST T alterations in the left precordial leads were observed in 65 2 per cent of the cases in 20 per cent these changes could not be attributed to digitalis intake This factor, fairly common in our series was found in cases with aortic obstruction [28] We think that these alterations whether brought about by digitalis intake or not, are the result of a volume overload of a left ventricular cavity receiving both the pulmonary and systemic venous flows

Abnormal initial QRS forces directed toward the left anteriorly have been ob served in 43 4 per cent of our material As reported,[19 21 23] these alterations were more frequent in L loop cases Neverthe less in our material the highest incidence was in cases associated with pulmonary stenosis (85 9 per cent) regardless of the nature of the bulboventricular loop

The QRS was mostly located close to +120 degrees In accordance with previous contributions,[3 19 20] left axis deviation was more frequent in D loop cases

As established [1 22] the QRS axis and frontal and precordial morphologies were sometimes indistinguishable from those of tricuspid atresia cases

In accordance with further se ries [3 7 18 20 23 29] other associated malforma tions did not significantly alter the QRS axis

The earlier finding of discord between the QRS axis and the pattern of ventricular hypertrophy[3 19 20 23 29] did not prove statis tically significant in our series as it was applicable only in three D loop and in two L loop cases

Deep Q waves in Leads II III and aV_F were present in 30 4 per cent of the cases Similar to prior recordings [23 30] these were more frequent in L loop cases

An atrioventricular bl[illegible] of advanced

QRS	Deep Q III aVF	aVR	Isodiphasism	ST T changes	Ventricular pattern	B V loop pulmonary outflow tract
+120	—	QS	—	+	LVH	L Loop—with P A
- 90	—	qR	—	—	RVH	L Loop—with P S
+ 10°	—	rS	rS	—	LVH	L Loop—with P S

QRS	Deep Q III-aVF	aVR	Initial vector of QRS	Isodiphasism	ST T changes	Ventricular pattern	B V loop pulmonary outflow tract
80	—	qR	LP	—	+	RVH	D Loop—without P S
160	—	qR	LP	—	+	RVH	D Loop—with P S
90	—	qR	LA	+	+	RVH	D Loop—without P S
180	—	qR	LA	—	—	RVH	D Loop—with P S
+150	—	qR	LP	—	—	RVH	D Loop—with P S
und	—	QR	LA	+	+	BVH	D Loop—without P S
+150	—	QR	RA	—	+	BVH	D Loop—without P S

degree (Fig 4) was observed in one L loop case This has appeared more frequently in L loop cases [18 20 28 30 31]

Accelerated atrioventricular conduction was found in three cases two of which presented with a discordance between the position of the aorta (anterior and right sided respective of the pulmonary artery) and the type of bulboventricular loop (L loop)

Summing up we believe that single left ventricle cannot be electrocardiographically diagnosed Nevertheless an electrocardiogram showing an essentially negative QRS morphology in Lead aV_R ST T alterations in the leads facing the left ventricular free wall and stereotyped QRS morphology (RS or rS) in the entire precordium make this anomaly suspect A typical patent ductus arteriosus transposition of the great arteries with a large systemic shunt tricuspid atresia and myocardiopathies must be considered in the differential diagnosis

In cases with increased pulmonary blood flow P waves are generally taller in tricuspid atresia than in single left ventricle There is a higher incidence of left atrial hypertrophy in myocardiopathies and in patent ductus arteriosus in relation to single left ventricle

Group I Dextrocardia A QRS morphology inversion between Leads I and aV_R was found in the dextrocardiac group In contrast a similar inversion has not been found in L loop cases with the cardiac apex pointing towards the left. The existence of P waves suggesting biatrial enlargement is worth emphasizing despite the presence of severe obstruction to the pulmonary outflow tract

Group II The electrocardiographic findings in this group were in good accord[14 18 19] with the relative ventricular size a right ventricular hypertrophy having been diagnosed in Subgroup A and B cases There was a biventricular enlargement in Group C and in the special case The QRS axis was uniformly directed towards the right

In contrast to Group I an essentially positive deflection in Lead aV_R prevailed in this group [3 8 12 14]

The abnormally posterior and leftward orientation of the initial QRS forces in these cases (87 5 per cent) was attributed to an accentuated right ventricular hypertrophy

We suggest that when considering an

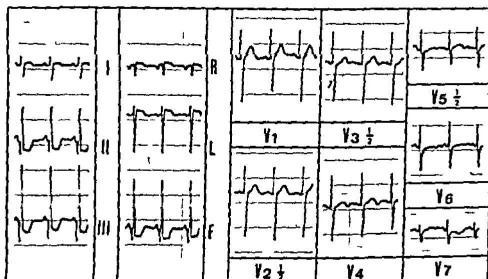


Fig 9 Electrocardiogram showing a QS complex in aV_R RS complexes through V_1 to V_6 and ST T changes in Leads II III aV_F and the precordial leads Case 19 (age = 1 day)

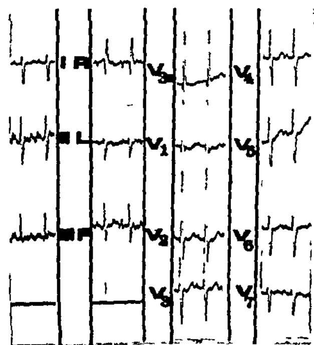


Fig 10 Accentuated right ventricular enlargement in one II A case Note the presence of q waves through V_3r V_3 and the important terminal forces in Lead aV_R Case 28 (age = 19 days)

electrocardiogram showing an accentuated right ventricular enlargement with an essentially upward deflection in Lead aV_R and q waves through V_3r V_1, V_2 and V_3 the diagnosis of the single right ventricle should be taken into account Other conditions having a bearing on the differential diagnosis would include mitral atresia double outlet right ventricle, severe right ventricular outflow obstructions, and total anomalous pulmonary venous drainage

Summary

A review is made of the electrocardiographic findings of 33 cases with derangement in the spatial relationship between the ventricular septum and the atrioventricular canal

To obtain an analysis with a maximal homogeneity six groups are established according to the extent and direction of the above mentioned derangement (Table I) Groups IA and IIA are equivalent to the most frequent designations of single left and right ventricle respectively or more exactly to those of double inlet left and right ventricle

Cases with disturbance in the position of the heart are considered separately to ascertain whether the outflow obstructions and the bulboventricular loop influence the electrocardiographic morphologies in any way

Electrocardiographic features of the other four groups (Table I) are analyzed to determine if the differences in the relationship between the atrioventricular canal and the interventricular septum are of small degree and therefore if the hypoplastic cavity becomes larger

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Radiological patterns of obstructive cardiomyopathy of the left ventricle in childhood

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Subaortic muscular stenosis or obstructive cardiomyopathy of the left ventricle is a well known disease in adults but few reports concern children and infants We have collected nine cases four of which were in infants of 3, 6 11 and 18 months, and five in children of 3 4, 5, 5½ and 6 years respectively

Obstructive cardiomyopathy is generally idiopathic and often familial It is sometimes associated with stenosis of the aortic outflow tract A systolic murmur was present in all cases In infants cardiac failure may be the first symptom In children the murmur may be discovered at routine examination or the child may present with dyspnea and even syncope in some cases The systolic murmur is ejection like, variable and best heard at the apex The ECG may show signs of left ventricular hypertrophy or of biventricular hypertrophy if the cardiopathy is bilateral We have observed 6 cases of primary cardiomyopathy of which 2 in infants were biventricular, and 3 cases of secondary cardiomyopathy in children, of the latter one was in a case of aortic valvular stenosis the second a case of subvalvular (diaphragmatic) aortic stenosis, and the third a case of both valvular and subvalvular stenosis

The frontal view (Table I)

In the 4 cases in infants the cardiothoracic index was above 0 55, the mean at this age In the 5 cases in children the index is superior to the normal mean of 0 45 In all cases there was cardiomegaly The inferior left cardiac segment was convex and the apex was displaced laterally (Fig 1) these signs of left ventricular hypertrophy were noted in 8 out of 9 cases Angulation of the left superior border as described by Wigle and Vernant was seen in only one case, an infant of 6 months

Angiocardiography

A ventricular systolic pressure gradient was present in all cases Angiocardiography and left cineangiography were performed with a catheter introduced by way of a retrograde arterial route Frontal, right anterior oblique and lateral views were taken The left ventricle looks abnormal being distorted with a very thick wall

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Table I Chest film—frontal view

Patient no	*Age*	*Cardiothoracic index*	*Apex*	*Left inferior segment of the heart*
1	18 months	0 62	much displaced laterally	convex
2	3 months	0 62	much displaced laterally	markedly convex
3	6 months	0 63	much displaced laterally	markedly convex
4	11 months	0 64	displaced laterally	markedly convex
5	6 years	0 60	displaced laterally	normal
6	3 years	0 60	displaced laterally	convex
7	5½ years	0 52	displaced laterally	markedly convex
8	5 years	0 48	not displaced	convex
9	4 years	0 54	displaced laterally	markedly convex



Fig *1* Typical chest x ray of infant with cardiomyopathy The *inferior left* cardiac segment is convex and the apex is laterally displaced



Fig 2 Border abnormalities in 11 month old *infant* with abnormal left ventricle There is an indentation of the left border of the upper *portion of the left* ventricle and also of the inferior margin associated with eptal hypertrophy

A The morphologic or qualitative aspects

1 THE ABNORMALITIES OF THE BORDERS We noted an indentation of the left border of the upper part of the left ventricle and of the inferior margin in 7 out of the 9 cases (Fig 2) These indentations were associated with septal hypertrophy and were visible in both diastole and systole The apex was not delineated or was to a lesser degree tapered in 5 out of the 9 cases

2 THE INTERNAL APPEARANCE OF THE VENTRICULAR CAVITY *Hypertrophy of the mitral papillary muscles is usual* (Figs 2 and 3) The anterior one looked very hypertrophied in 6 cases and the posterior muscle looked very hypertrophied in 7 cases out of the 9

This sign is not specific but is very common and is easily visualized If the axis of the papillary muscles is displaced to the left or upward instead of being continuous with the mitral axis this is of high diagnostic value This distortion of the papillary muscles causes abnormal traction on the chordae tendineae and the mitral valve anterior leaflet cannot move backward during systole The outflow tract is obstructed during meso and telesystole

The mid ventricular stenosis in systole is evident *in* 7 cases out of 9 cases (Fig 3) The ventricular cavity looks very small during telesystole in these cases and is

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Table II *Thickness of the left ventricular wall*

Manifestation	*Diastolic thickness (mm)*	*Systolic thickness (mm)*	*Systolic diastolic difference (mm)*	*Diastolic thickness* / *Aortic diameter (mm)*	*Systolic thickness* / *Aortic diameter (mm)*	*Cavity width* / *Diastolic thickness (mm)*	*Cavity width* / *Systolic thickness (mm)*
Cardiomyopathy	8 6	17 6	7 8	5 62	11 5	0 51	0 17
Normal left ventricle	5 5	8 5	3	3 19	4 95	0 94	0 52



Fig 5 Angiocardiogram showing mitral regurgitation in an 18 month old child This symptom was present in two of our patients

infants 10 2 mm in the children 3 to 6 years of age) compared with 5 5 mm for normal ventricles During systole the thickness of the left ventricle was 16 6 mm in the cardiomyopathies (15 mm in the infants and 19 mm in the children 3 to 6 years of age) compared with 8 mm for normal ventricles In order to remove the factor of age we calculated the relationship between the mean diastolic thickness and the aortic diameter The same relationship was calculated for the systolic thickness In diastole the mean ratio was 5 62 (normal 3 19) and in systole 11 5 (normal 4 95) Finally the relationship between the difference between mean diastolic and mean systolic thickness and the aortic diameter was 5 9 in the cardiomyopathies compared with 1 74 for normal ventricles In their series of adults Levine and Braunwald



Fig 6 Angiogram of 18 month old infant with cardiomyopathy Infundibular stenosis is apparent on the right with stasis in the dilated inflow tract

studied the relationship between the width of the ventricular cavity and the wall thickness and noted that it was much smaller in cardiomyopathies than in valvular stenosis Our own results show values of 0 51 in diastole and 0 17 in systole for cardiomyopathies whereas measurements on normal ventricles gave values of 0 94 and 0 52 respectively

In conclusion angiography of the left ventricle in infants and children with cardiomyopathy show similar signs to those found in adults The left ventricle is distorted with indentation of the margins and



Fig 3 Angiocardiogram showing the internal appearance of the ventricular cavity Hypertrophy of the mitral papillary muscles is evident and mid ventricular stenosis in systole is also evident



Fig 4 Angiocardiogram lateral view of a 6-year old child showing the pattern of an inverted cone which appeared very distinctly in two of our patients This manifestation is very diagnostic if seen in telesystole

moderately diminished in size *during diastole*

The characteristic feature of a radiolucent band crossing the outflow tract below the aortic ring, visible on frontal and lateral views in mesosystole and in telesystole was difficult to see in most of our cases

On lateral views we noted the pattern of an inverted cone (Fig 4) which was very distinct in two out of six cases clear in one, and absent in three cases If seen in telesystole it is highly diagnostic The cone is limited anteriorly by the hypertrophied septum and posteriorly by the anterior mitral leaflet which does not move backward during systole It can also be seen in diastole but must be differentiated from the false image of stenosis in diastole secondary to the opening of the anterior leaflet which comes close to the septum Finally, we noted mitral regurgitation in 2 cases (Fig 5)

B The quantitative aspects

We have tried to measure some of the abnormalities, in particular the thickness of the left ventricular wall Firstly the longitudinal axis of the ventricle is altered and an angulation of 167 degrees (mean value) was seen as compared with 179 degrees for 9 normal ventricles (in infants and children of the same age) The reduction of the systolic capacity is marked at the middle segment of the left ventricle in both absolute and relative terms In order to establish this fact we have measured the *relationship* comparing the difference between the diastolic and systolic widths of the ventricular cavity with the diameter of the aorta In normal ventricles this ratio was 0 41 but in the patients with obstructive cardiomyopathy the mean value was 0 81 The thickness of the left ventricular wall at the middle section of the free left margin on frontal views appeared much greater in the cardiomyopathies than in the normal left ventricles (Table II) During diastole the mean thickness was 8 6 mm in the cardiomyopathies (7 mm in the

Embolic coronary artery occlusion in percutaneous transfemoral coronary arteriography

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Although the technique of selective coronary angiography as described by Sones and Shirey[1] has been in popular use since 1962 and has enjoyed a record of relative freedom from major complications, its few limitations, including occasional poor coronary opacification, difficulty with catheter introduction associated with anatomic arterial variations, or the inherent complexity of the procedure, together with the advent of coronary bypass surgery with the resultant demand for increasing numbers of studies, have led to a search for newer, more reliable techniques.

Among the alternatives, the technique of percutaneous transfemoral artery bilateral selective coronary arteriography as described by Judkins[2] has indeed seemed to resolve most of the problems previously encountered.

With a recent exception,[3] previous reports of a major complication of coronary artery occlusion with myocardial infarction due to emboli introduced with this technique did not prepare us for its startling frequency in our laboratory.[4,5,6]

Methods and materials

Selective coronary arteriography was carried out in 215 patients from April 1970 to May 1972 (147 men and 68 women whose ages ranged from 30 to 70 years, with a mean age of 52 years). The Sones technique was used in 76 and the Judkins technique was used in 139. During the Judkins technique a No. 18 gauge thin walled arterial needle was employed for percutaneous entry of the common femoral artery. Teflon coated 145 cm. guide wires were used and, where necessary, a Safety J guide was employed.

A short 7 F Teflon catheter was inserted into the artery over the guide before inserting the pig tail catheter used for the

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a reduced systolic capacity. The thickness of the free wall of the left ventricle is increased and in infants may exceed 5.5 mm in diastole and 8.5 mm in systole. In the biventricular cases, right ventricular anomalies may also be seen. The right ventricle is usually displaced because of the septal hypertrophy and enlargement of the left ventricle. In infants, infundibular stenosis may be seen on the right with stasis in the inflow tract which is often dilated (Fig. 6). In these biventricular cases the thickness of the septum may be measured by means of simultaneous opacification of both ventricles with a right catheter and 2 separate injections (see Robicsek and associates).

Differential diagnosis

In children cardiomyopathy may be confused with muscular hypertrophy of the left ventricle as seen in Friedreich's ataxia or with the tumor-like hypertrophies associated with tuberous sclerosis of Bourneville's glycogen storage disease or Refsum's disease. The clinical picture may be more valuable than radiology in differentiating the hypertrophic cardiomyopathies from the obstructive cardiomyopathies either idiopathic or secondary to a congenital stenosis of the aortic outflow tract.

Summary

The authors report 9 cases of obstructive cardiomyopathy of the left ventricle in childhood. Angiograms performed by the Seldinger technique showed the characteristic radiological features of the disease which may be either idiopathic in origin or associated with an aortic stenosis.

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and/or ischemic pap llary muscle dysfunction she was admitted to the hospital in October 1971 for cardiac catheterization and selective coronary arteriography

During selective injection of the left coronary artery using the percutaneous transfemoral approach she suddenly developed chest pain accompanied by cardiovascular collapse She was found to have a block of the left main coronary artery at its bifurcation into the circumflex and anterior descending branches (Fig 1) Resuscitation attempts precluded recording her electrocardiogram at this particular t me and despite all efforts the patient died on the catheterization table

Postmortem examination revealed an atherosclerotic narrowing of greater than 80 per cent prior at the bifurcation of the left main coronary artery into the left anterior descending and circumflex branches which was occluded by a fresh clot Findings compatible with the syndrome of ballooning mitral valve were present

Patient 2 A 56-year old white man was first admitted to the Duval Medical Center in August 1969 presenting a six month history of progressively more severe and frequent substernal chest pain which radiated to the left arm and was usually relieved by rest

Physical examination was within normal limits and after serial electrocardiograms and enzyme determinations were unremarkable he was discharged with a diagnosis of coronary insufficiency

After readmi sion in April 1970 us ng the Sones technique bilateral selective coronary arteriography demonstrated 70 per cent narrowing of the right coronary artery and complete occlusion of the left anterior descending artery beyond the first diagonal branch with retrograde filling from the right coronary artery In June 1970 an aorto-left anterior de cending artery saphenous vein bypass procedure was performed successfully

After one year free of anginal symptoms he was readmitted in August 1971 for restudy of his bypass graft Using the percutaneous transfemoral ap p oach injection into the bypass revealed graft patency but injection into his left main coronary artery was followed immediately by bradycardia and complete AV block accompanying embolic occlu ion of the left main coronary artery (Figs 2 and 3) A pacemaker was positioned in the catheterization laboratory however after transfer he died in the Coronary Care Unit in cardiogenic shock Permi ion for autopsy was not granted

Patient 3 In January 1970 a 32 year old wh te man began exper enc ng severe sub ternal che t pain which radiated to both shoulders was occasionally accompanied by pallor bore no relation hip to exer tion and wa rarely relieved by nitroglycer n He smoked one package of c garettes da ly for 20 years and family h story contained evidence of coronary artery d sease

In M il 1970 after a normal admission physical examin tion percutaneous tran femoral select ve coronary arter ography was carried out On inject on 1 to the left coronary artery the di tal left anter or descend n artery seemed to be totally blocked about 2 cm beyond it or gin (F g 4) Accompany i g th the monitor revealed pronounced anterior ST segment and T wave elevation and because of the persistent pain the procedure was terminated without injection of the right coronary artery

He was transferred to the Coronary Care Unit and had an uneventful recovery from an anterior myocardial infarction confirmed by electrocardiogram but he continued to complain of substernal chest pain identical to that for which he was first adm tted

Patient 4 A 53 year old Negro male construction worker was admitted to the University Hospital in May 1972 presenting a h story of precordial chest pain relieved within 10 minutes by nitroglycerin for approximately five years more frequent since December 1971 He had smoked more than two pack ages of cigarettes daily for more than 20 years before stopp ng 6 to 8 years prior to admission and was known to be hypertensive for 4 years treated sporadically Phy ical examination disclosed a blood



Fig 2 Patient No 2 Percutaneous transfemoral injection of the bypass graft left anterior oblique projection Prior to injection of the left main coronary artery all three branches of the left coronary system were patent



Fig 3 Patient No 2 Percutaneous transfemoral left coronary arteriography left anterior oblique projection Injection into main left coronary artery demonstrated complete block of the left main coronary artery (Catheter was retracted after injection)



Fig 1 Patient No 1 Percutaneous transfemoral left coronary arteriography left anterior oblique position Injection of the left main coronary artery revealed total obstruction proximal to bifurcation into the left anterior descending and circumflex branches

left ventriculogram Ducor Judkins preshaped disposable right and left coronary catheters were used for the coronary study [2] Selective studies were done with the patient in different oblique projections Contrast material was injected by hand syringe and pressures were monitored by the stop cock system described by Sones and Shirey [1] Flushing of the coronary catheter which was continuously infused with heparinized saline was made at the level of the descending aorta before it was advanced toward the ascending aorta At the present time the left coronary catheter is removed from the coronary ostium after each injection aspirated, and is flushed before reinsertion If right side cardiac catheterization is not performed an intravenous catheter is placed in the left arm before the procedure for use in emergency situations Pressures were monitored with P23Db Statham pressure transducers and mean artery pressure was obtained by electronic filtering Lead II of the electrocardiogram was continuously inscribed on all records All tracings were inscribed by a 16 channel Electronics for Medicine DR 16 physiological Recorder

Following the procedure the patients were admitted to the Coronary Care Unit for 24 hours during which time they were monitored continuously and vital signs were taken periodically An electrocardiogram was taken the following day before the patient was discharged

If, because of clinical angiographic electrocardiographic findings a cardiac complication was suspected serial enzymes and electrocardiograms were obtained

Results

We have done 139 selective coronary studies via the percutaneous transfemoral artery approach from April 1970, to May 1972 Approximately 1 112 injections were made into the coronary arteries during these studies

During the procedure acute myocardial infarction probably due to embolic occlusion within the left coronary artery system occurred in 6 patients Of these patients No 1 and 2 died with total occlusion of the left main coronary artery shortly after the procedure

Postmortem examination obtained in Patient 1 disclosed a fresh clot obstructing the left main coronary artery at the site of severe atherosclerotic narrowing In the case of Patient 2 consent for autopsy was not obtained

Patient 3 developed total occlusion 1 cm distal to the origin of the left anterior descending coronary artery after the first injection Patient 4 also developed total occlusion of the left anterior descending coronary artery at the junction between its middle and distal thirds Both patients experienced uneventful recovery from clinical evidence of acute myocardial infarction

Patients 5 and 6 both suffered total occlusion of the left circumflex coronary artery In both there was also uneventful recovery from clinical evidence of acute myocardial infarction

Case reports

Patient 1 A 62 year old white woman diagnosed in 1967 as having Turner's syndrome (X045 XX 46 mosaic by chromosome analysis) was followed at the Duval Medical Center since 1965 for mild congestive heart failure associated with chest pain relieved within 5 to 10 minutes by nitroglycerin

In 1967 a short late systolic murmur with mid systolic click was described Although the electrocardiogram was within normal limits Master test demonstrated subendocardial injury during and immediately after exercise

As she was felt to have balloon mitral valve



Fig 7 Patient No 5 Percutaneous tran femoral left coronary arteriography right anterior oblique projection First injection demonstrated patency of all three vessels of the left coronary system Note minimal disease of left anterior de cend ng coronary artery



Fig 9 Patient No 6 Percutaneous tran femoral left coronary arteriography left anterior oblique projection First injection demon trated all three branches of the left coronary artery system to be patent



Fig 8 Patient No 5 Percutaneous tran femoral left coronary arteriography right anterior oblique project on Fourth injection demon trated block of left circumflex coronary artery



Fig 10 Patient No 6 Percutaneous transfemoral left coronary arteriography left anterior oblique projection Third injection demonstrated block of left c rcumflex coronary artery

In January 1972 follow ng a normal physical exam nat on percutaneous tran femoral bilateral select ve coronary arterio raphy was carried out in which a mall right coronary artery was found occl ded and the left anterior descending coronary artery was found to be mildly diseased Following the third injection into the left main coronary ar tery he developed hypote i on and bradycardia compan ed by electrocard ographic e idence of infer or wall njury There wa noted to be complete ob t uction of the left circumflex coronary artery wh ch h d not been seen n the prev ou injecti n in the same projection (Fig 9 and 10) He wa trans ferred to the Coron ry Care Unit where his serial enzyme rose an d electrocard ographic evidence of po tero-diaphragmatic my cardi al nfarction de velo ed

Discussion

We had used almost exclusively the technique of selective coronary arteriography described by Sones and Shirey [1] but in 1970 we started using the percutaneous transfemoral technique[3,4] in the following situations

1 tortuous subclavian innominate arteries

2 difficulty in obtaining satisfactory coronary opacification

3 previous cut-downs in the brachial artery with faint pul e



Fig 4 Patient No 3 Percutaneous transfemoral left coronary arteriography left anterior oblique projection Injection into the left main coronary artery disclosed total block of left anterior descending coronary artery It should be noted the left main coronary artery and the left circumflex coronary arteries are patent

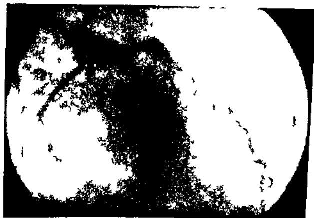


Fig 5 Patient No 4 Percutaneous transfemoral left coronary arteriography right anterior oblique projection Normal left coronary system



Fig 6 Patient No 4 Percutaneous transfemoral left coronary arteriography right anterior oblique projection Third injection demonstrated complete block of left anterior descending coronary artery

pressure of 160/90 an accentuated though physiologically split second sound an audible fourth sound and a nonradiating Grade I short systolic murmur at the cardiac apex

Having during bilateral selective coronary arteriography via the percutaneous transfemoral approach demonstrated normal right left main circumflex coronary arteries the patient developed substernal chest pain after the third injection into the left main coronary artery Acute occlusion of the distal left anterior descending coronary artery was found (Figs 5 and 6) accompanied by ST segment elevation in the anterior and inferior leads followed later by evolving electrocardiographic changes

Following the procedure he was admitted to the Coronary Care Unit and recovered uneventfully from an acute myocardial infarction due to embolic occlusion of the anterior descending branch of the left coronary artery

Patient 5 A 56-year old white man was admitted to University Hospital in January 1972 for selective coronary arteriography having in 1960 begun experiencing substernal chest pain which radiated into the left arm occurred with exertion and anxiety and was relieved within 5 to 10 minutes by nitroglycerin

For two and one half years he had had symptoms compatible with paroxysmal nocturnal dyspnea two or three pillow orthopnea and occasional exertional dyspnea during which time he was maintained on digitalis and diuretics Hypertension known present for four years had been treated for three years He had smoked 2 to 3 packages of cigarettes daily for 12 years stopping 10 years prior to admission He was said to have had an elevated cholesterol and an abnormal glucose tolerance test A brother and sister both 58 reportedly died of myocardial infarction and a brother 60 was said to have angina

On physical examination blood pressure was 140/80 the optic fundi presented Grade II arteriosclerotic changes and there was an apical fourth sound

On undergoing percutaneous transfemoral bilateral selective coronary arteriography in which the right coronary artery was within normal limits and the left anterior descending coronary artery displayed mild disease he sustained an embolus to the left circumflex artery on the fourth injection into the left main coronary artery (Figs 7 and 8) He was admitted to the Coronary Care Unit and after 14 hospital days was transferred to the Veterans Administration Hospital for continued convalescence from myocardial infarction

The acute episode was unaccompanied by diagnostic electrocardiographic changes but infarction was reflected by marked rise in the serum enzyme

Patient 6 A 52 year old white man was admitted to another hospital in December 1971 because of acute onset of substernal chest pain Serial electrocardiograms demonstrated stable nonspecific ST T changes and after the usual studies ruled out acute myocardial infarction he was felt to have angina pectoris Following discharge recurrent substernal pain brought on by exertion was partially relieved within 5 to 10 minutes by nitroglycerin After institution of isosorbide and propranolol he became essentially symptom free

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Fig 7 Pat ent No 5 Percutaneous transfemoral left coronary arterio raphy right anterior oblique projection Fir t injection demon trated patency of all three vessels of the left coronary sy tem Note minimal disease of left anterior descending coronary artery



Fig 9 Patient No 6 Percutaneous transfemoral left coronary arteriography left anterior oblique projection First injection demonstrated all three branches of the left coronary artery system to be patent



Fig 8 Pat ent No 5 Percutaneous tran femoral left co onary arteriography right anterior oblique p ojection Fourth inject on demon trated block of left circumflex coronary artery



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Discussion

We had used almost exclusively the technique of selective coronary arteriography described by Sones and Shirey [1] but in 1970 we started using the percutaneous transfemoral technique[3 4] in the following situations

1 tortuous subclavian innominate arteries

2 difficulty in obtaining satisfactory coronary opacification

3 previous cut-downs in the brachial artery with faint pulse

4 young females with spastic brachial arteries

However because the procedure is quickly learned by trainees fluoroscopic time is abbreviated, and good coronary visualization is obtained, its use in our laboratory had recently been greatly expanded

With one exception [3] our incidence of the procedural complication of myocardial infarction due apparently to embolic occlusion within the left coronary artery system appears to differ significantly from that reported by others though the problem may have been associated with left anterior descending artery occlusion described by Gau and colleagues[5] and left circumflex coronary artery occlusion reported by Cheng and associates [6]

This potentially hazardous complication has, however been previously reported [3 6 9] In order to minimize the risk it was first recommended that the catheter be energetically flushed prior to advancing the tip from the descending to the ascending aorta and, later if more than the usual time between the injections is required if persistent electrocardiographic changes occur or if the patient s position must be changed the catheter should be removed from the ostium of the coronary artery aspirated and flushed before another injection is carried out [7]

However, since two more cases have recently occurred in our laboratory despite meticulous observation of these modifications in technique we have elected to repeat this maneuver after each injection

The severity of the infarction apparently bears close relationship to the size of the embolus the level of the obstruction and the previous state of the coronary arteries A small fibrin clot will probably not obstruct the main coronary artery or the initial segments of the primary branches unless there is a severe narrowing at these levels as was the case in Patients 1 and 2

In none of our patients was damping of the pressure noted prior to injection of contrast media into the left coronary artery—indicating that the presence of a good pressure is not a reliable sign of the absence of a clot in the catheter tip

The high incidence of this complication in our laboratory may, in part, be explained by the fact that during the first part of this study, none of the recently suggested precautions were employed However since the last cases occurred despite the use of all theretofore recommended modifications it is felt this type of accident may be related to the nature of the left coronary catheter (possibly the increased angulation of the catheter tip), or to the sequence in which it is used

The problem might be reduced by withdrawal and flushing of the catheter between each injection This would however negate much of the procedural advantage (that of minimizing fluoroscopic and procedure time) and would increase the time in which a fibrin clot might form as well as predispose to other complications such as subintimal coronary dissection [5 10] or perforation of the coronary artery [11]

Recently, use of the guide wire and or insertion of the second catheter has been causally implicated Use of Teflon sheaths rather than wires and systemic anticoagulation have therefore been suggested as reasonable modifications with which to reduce the incidence of this complication [1]

At the present time we are however again limiting the transfemoral approach to only the indications previously outlined and would suggest this procedure might be less innocuous than its previous acceptance indicates

Summary

A review is presented of 139 selective coronary artery studies during a 25 month period in which 1 112 coronary artery injections were performed using the percutaneous transfemoral artery approach as described by Judkins in 1967 [2] Six patients (four per cent) developed acute occlusion of the left coronary artery or one of its branches during the procedure and two of these died with occlusion of the left main coronary artery shortly thereafter

It is felt that since in all cases of this series and most of those of others embolic occlusion within the left coronary artery system occurred the complication is related to the thrombogenic properties of the left coronary catheter or to the procedure in which introduction of the second catheter is required

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Asymptomatic electrocardiographic alterations in sarcoidosis*

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Although sarcoidosis is not a rare disease clinical recognition of intrinsic involvement of the heart is infrequent This is irrespective of the finding that up to 20 per cent of patients with sarcoidosis at postmortem can be demonstrated to have some degree of myocardial involvement [1,2] As of 1971 however only 70 cases of documented clinical involvement of the heart in sarcoidosis have been reported in the literature The major manifestations of intrinsic cardiac involvement have been conduction disturbances disorders of impulse formation and progressive myocardial failure [1,3,6]

Recently we observed an unusual aggregation of patients with suspected cardiac sarcoidosis at the Sarcoidosis Clinic of The Mount Sinai Hospital These patients had potentially life threatening episodes requiring hospitalization in a cardiac intensive care unit where they were continuously monitored A review of these specific cases will be reported in detail in a separate publication

The appearance of these serious cardiac complications prompted us to survey systematically over a three month period of time the electrocardiographic findings of unselected asymptomatic patients seen routinely in the Sarcoidosis Clinic in an attempt to document possible asymptomatic myocardial involvement that may herald significant cardiac disease

Patient material

In addition to the usual clinical radiologic and laboratory investigations for the presence of tissue confirmed sarcoidosis these patients were scrutinized with special attention to possible cardiac abnormalities. Patients were included in the study only if the following criteria were present (1) under forty years of age (2) no past or present history of cardiac or hypertensive vascular disease (3) absence of a murmur on physical examination (4) no history of current or past cardiotonic or antihypertensive regimens and (5) absence of cardiomegaly on x ray Eighty patients satisfied all of the above criteria Twelve lead electrocardiograms (ECG s) with 30 second Lead II rhythm strips were performed on each patient using Hewlett Packard A1500 ECG machines The ECG s were read independently by three cardi

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Table I *Electrocardiographic alterations in 80 patients with sarcoidosis*

	Patients with abnormal ECG — No of patients (41)	Patients with normal ECG — No of patients (39)	Total patients
Sex			
Male	15	14	29
Female	26	25	51
Ethnic group			
Black	35	26	61
Puerto Rican born	4	10	14
Caucasian	2	3	5
Estimated duration			
Subacute	17	16	33
Chronic	24	23	47
Chest x ray			
Stage I	19	13	32
Stage II	13	18	31
Stage III	9	8	17

ologists and were classified according to type of abnormality ST segment changes were considered to be significant if altered by 1 mm or more QT intervals were corrected for rate The records were then reviewed with any discrepancies in interpretation subjected to discussion and final consensus

All patients were classified as to the duration of sarcoidosis—i e subacute or chronic—and according to stage on the basis of chest x ray findings as described by Siltzbach [8]

Results

There were 51 women and 29 men (Table I) 61 were black 14 were Puerto Rican and 5 were Caucasians Subacute sarcoidosis (of less than 2 years duration) existed in 33 patients and chronic sarcoidosis in 47 patients Chest x rays at the time the electrocardiograms were performed showed hilar adenopathy alone (Stage I) in 32 patients hilar adenopathy with parenchymal mottling (Stage II) in 31 patients and mottling only (Stage III) in 17 patients

Some electrocardiographic abnormality was detected in 41 of these 80 patients without accompanying cardiac symptoms They exhibited in all 57 separate deviations from normal Abnormalities in rhythm and conduction were seen in 18 instances occurring [illegible] ents (Table II) First degree heart block was noted in 7 patients a shortened PR interval in 5 Intra atrial conduction defects were seen in 2 patients and premature atrial contraction in one One patient presented with AV dissociation one with ventricular premature contractions and one with AV dissociation with junctional premature contractions

There were also 39 repolarization abnormalities among 26 of the patients in this study (Table III) T wave changes were noted in 21 instances and consisted of flat T waves in 5 inverted in 6 notched in 9 and peaked in 1 U waves in the absence of a bradycardia were seen in 9 patients ST segment elevation greater than 1 mm occurred in 4 patients with ST depression of equal magnitude noted in 4 others One patient had a prolonged QT interval after correction for rate

Factors including sex of the patient ethnic background and duration of sarcoidosis radiographic stage and corticosteroid therapy did not appear to influence the frequency and character of the electrocardiographic abnormalities which were found None of the patients observed in this study exhibited clinical evidence of cardiac disease during a six month period of subsequent observation

Discussion

In the present study greater than 50 per cent incidence of minor ECG changes in

Table II. Alterations in rhythm and conduction in 15 of 80 patients with sarcoidosis

Alterations	No. of patients
PR intervals	
>0.20 sec	7
<0.12 sec	5
Intra-atrial conduction defects	2
Premature atrial contractions	1
A-V dissociation	1
Ventricular premature contractions	1
A-V dissociation with junctional premature contractions	1

Table III. 39 repolarization abnormalities in 26 of 80 patients

	No. of patients
Flat T waves	5
Inverted T waves	6
Notched T waves	9
Peaked T waves	1
U wave (no bradycardia)	9
ST segment elevations	4
ST segment depressions	4
Prolonged QT interval	1

young sarcoidosis patients was found. The significance of these alterations and its relation to clinically manifest cardiac sarcoidosis is not obvious. The nature of the underlying histopathological myocardial changes that may account for these changes in asymptomatic individuals is also unclear. The most plausible hypothesis would seem to be the fortuitous but strategic placement of sarcoid granulomas within various locations of the cardiac conducting system as simply another representation of systemic involvement in this disorder. Such a hypothesis is supported by findings of granulomas in the cardiac conducting system of patients succumbing to fatal arrhythmias.[3,4,6,7] Whether or not myocardial granulomas have a predilection for the conducting system cannot be answered from available autopsy data or from clinical studies. Numerous granulomas are almost invariably found at autopsy in the cardiac muscle as well as in the more usual locations, suggesting that involvement of the conduction system occurs haphazardly in a hit or miss fashion.[2,5]

The most common electrocardiographic findings reported in cases of myocardial sarcoidosis are conduction disturbances and arrhythmias consisting of frequent premature ventricular contractions, paroxysmal atrial and ventricular tachycardias, and disturbances in sinoatrial function.[9,11] However, on occasion extensive involvement of the myocardium has been seen associated with only minor ST segment and T wave changes noted on the electrocardiogram.[11] In one instance, the electrocardiogram in a patient with extensive myocardial sarcoidosis revealed only the presence of a sinus tachycardia.[13]

In the literature, up to two thirds of those patients whose deaths are considered to be directly related to intrinsic cardiac sarcoidosis died suddenly.[1,14] In 25 per cent of these fatalities no previous cardiac symptoms have been experienced. The average age at the time of death varied from 35 to 44 years.[4,15] Porter[4] reported fatal cardiac sarcoidosis to be twice as frequent in men as in women. However, in a series published by Mayaji and colleagues[15] the frequency in the two sexes was found to be reversed. In the asymptomatic patients of our study abnormal ECG findings were equally common in both sexes.

The mechanisms leading to sudden cardiac death in sarcoidosis have not been conclusively demonstrated. However, it is not unlikely that the presence of fatal arrhythmias is the common mode of exitus. It is known that individuals with abnormalities of repolarization may be more prone to develop arrhythmias through re-entry phenomena or by initiation and persistence of ectopic foci.[16,17] Twenty-six of our 80 patients demonstrated repolarization abnormalities, a potentially dangerous manifestation. Fifteen patients or 18 per cent had changes in rhythm and conduction which might also represent a threat of future difficulty. The ECG alterations here reported did not correlate with the ethnic group, the duration of sarcoidosis, the severity of pulmonary sarcoidosis as determined by chest x-ray staging, or treatment with corticosteroids in low dosage.

It is difficult to prove that these electrocardiographic changes are [illegible] result

of myocardial involvement without histologic evidence However the age of the patients studied the absence of a past or present history of treated or untreated hypertension or heart disease and the presence of a normal sized heart on chest film make other pathogenic mechanisms less likely In a large series of patients with proven myocardial sarcoidosis reported by Gozo and associates[18] Porter[4] and Bashour and colleagues[3] the electrocardiographic disturbances in rhythm and conduction which they described are similar to those seen in our series of patients

Reversibility of cardiac involvement has been known to occur and the suggestion has been made that early corticosteroid treatment of active granulomatous discease may lead to healing of the granulomas without subsequent fibrous scarring of the myocardium[4] The importance of early discovery and careful follow up of cardiac involvement in sarcoidosis is evident Early identification of patients at greatest risk may prove quite rewarding

At the present time prospective studies are under way in our clinic to determine which of the asymptomatic electrocardiographic abnormalities occurring in patients with sarcoidosis may represent precursors of more serious and potentially dangerous cardiac arrhythmias secondary to extensive myocardial involvement by sarcoid granulomas

Summary

Among 80 patients with tissue confirmed sarcoidosis attending the sarcoidosis clinic of the Mount Sinai Hospital electrocardiographic abnormalities of varying degree were noted in 41 patients despite the fact that these patients were entirely without cardiac complaints and exhibited no evidence of previous or current cardiac disease on thorough examination All these patients were under 40 years of age

The ECG alterations included repolarization abnormalities and alterations in rhythm and conduction Because of the potential hazards of some of these abnormalities prospective studies are being undertaken to determine which of them may represent precursors of dangerous intrinsic cardiac sarcoidosis

We are grateful to Mrs Maureen Baker and Miss Lynn Miller for their able technical assistance

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Table III 39 repolarization abnormalities in 26 of 80 patients

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Inverted T waves	6
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ST segment elevations	4
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Prolonged QT interval	1

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It is difficult to prove that these electrocardiographic changes are a result

nurse monitors stationed on medical wards use standardized self-coding sheets to record information on consecutively admitted patients. Data are collected on patient characteristics, diagnoses, the therapeutic efficacy of all drugs administered, as well as full details of dosage and duration of therapy. When drug treatment is instituted, the prescribing physician is interviewed to determine the therapeutic indications. Reasons for termination of therapy and descriptions of suspected adverse reactions are recorded as well. This report is based upon data gathered since 1966 on 13,349 hospitalized medical patients in nine hospitals in the United States, Canada, Israel, and New Zealand, of whom 268 (2.0 per cent) received propranolol during one or more admissions.

Results

The mean age of the 268 propranolol recipients was 55 years and 52.2 per cent were men. Thirty-two had a discharge diagnosis of acute myocardial infarction, 19 of rheumatic heart disease, 20 of thyrotoxicosis, and 11 of paroxysmal atrial tachycardia. A wide variety of cardiovascular disorders were represented in the discharge diagnoses of the other 186 patients. Fig. 1 shows the indications for propranolol therapy. Most patients received the drug for angina (115) or cardiac arrhythmias (98), while hypertension (31) and thyrotoxicosis (20) were less frequent indications. In 4 patients the reasons for therapy were not specified.

Other cardiovascular drugs were frequently administered concurrently with propranolol. They included nitrates (nitroglycerin, isosorbide dinitrate, pentaerythritol tetranitrate) in 99 patients, digitalis glycosides in 89, diuretics (thiazides, mercurials, furosemide, ethacrynic acid, spironolactone) in 69, antiarrhythmics (quinidine, procainamide, lidocaine, diphenylhydantoin) in 65, and antihypertensive agents (hydralazine, methyldopa, guanethidine, rauwolfia alkaloids, diazoxide) in 37. Many patients received several cardiovascular drugs concomitantly.

Seven of the 268 propranolol recipients died while in the hospital, but the drug was not specifically implicated in any of these deaths.

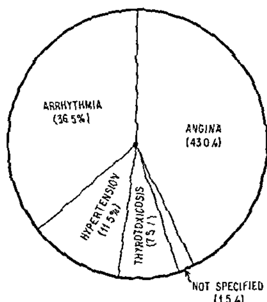


Fig. 1. Indications for propranolol in 268 patients.

Table I. Adverse reactions to propranolol among 25 patients

Life-threatening reactions	
Bradycardia and shock	3
Pulmonary edema	3
Complete heart block	1
Bradycardia and angina	1
Total	8
Non-life-threatening reactions	
Asymptomatic bradycardia	5
Neurologic disturbances	4
Hypotension and syncope	3
Asymptomatic hypotension	2
2:1 heart block	1
Fluid retention	1
Epigastric pain	1
Total	17
Total with adverse reactions	25

Adverse reactions attributed to propranolol were reported in 25 patients (9.3 per cent). These are summarized in Table I. Life-threatening reactions occurred in 8 patients and are detailed in Table II. In four of these cases the toxic reaction occurred within hours after propranolol was first administered. In three the onset of toxicity was delayed for several days. Case 2 first developed pulmonary edema three

Adverse reactions to propranolol in hospitalized medical patients A report from the Boston Collaborative Drug Surveillance Program*

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Propranolol an effective beta adrenergic antagonist was introduced in 1964[1] and is now a widely prescribed drug in clinical medicine It is extensively used either alone or in combination with other agents to treat cardiac arrhythmias of ventricular or supraventricular origin angina pectoris obstructive cardiomyopathies essential hypertension and thyrotoxicosis[2-4] Propranolol may also be of benefit in some patients with hyperkinetic heart syndromes[5] migraine headache[6] essential tremor[7,8] anxiety[9] psychoses[10] and septic shock[11,12]

Because of its ability to block beta adrenergic receptors propranolol can depress cardiac function of patients who are dependent on sympathetic stimulation For this reason it has been considered a potentially dangerous drug particularly in patients with severe heart disease or uncompensated congestive heart failure Yet there is little information regarding the frequency of adverse reactions to propranolol or the factors predisposing to toxicity This study presents data on adverse effects of propranolol based on observation of 268 hospitalized medical patients who received the drug

Patients and methods

The scope and operation of the Boston Collaborative Drug Surveillance Program have been described elsewhere[13-16] Trained

From the Boston Collaborative Drug Surveillance Program Boston University Medical Center and the Clinical Pharmacology Unit Massachusetts General Hospital Boston Mass This manuscript was prepared by Drs Greenblatt and Koch Weser

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Table III. Non life threatening reactions to propranolol

Case no.	Age (yrs)	Sex	Diagnoses	Indication for propranolol	Dosage	Time from initiation of therapy to onset of toxicity	Description of event
9	65	F	Ischemic heart disease, diabetes mellitus, hypertension	Hypertension	3[illegible]0 mg/day	4 days	While washing hands patient complained of headache then had syncopal episode
10	[illegible]0	F	Ischemic heart disease hypertension PAT	Arrhythmia	30 mg/day	2 days	Found to be excessively drowsy and sleepy Symptoms disappeared when drug was discontinued
11	24	M	Chronic glomerulonephritis, hypertension	Hypertension	240 mg/day	Hours	Intermittent lightheadedness and dizziness concurrent with beginning therapy
12	75	F	Ischemic heart disease acute MI	Angina	60 mg/day	4 days	Bradycardia (40-50/minute)
13	57	M	Ischemic heart disease, acute MI	Arrhythmia	40 mg/day	4 days	Gained 5½ lbs. due to fluid retention
14	[illegible]8	F	Diabetes mellitus, ischemic heart disease acute MI	Angina	30 mg/day	3 days	Blurring of vision
15	55	M	Hypertension	Hypertension	200 mg/day	21 days	Bradycardia (45/minute)
16	55	M	Ischemic heart disease	Angina	160 mg/day	9 days	Bradycardia (< 60/minute)
17	15	M	Cardiomyopathy PAT	Arrhythmia	120 mg/day	5 days	Hypotension ([illegible]0/45)
18	63	M	Recurrent PAT	Arrhythmia	30 mg/day	Hours	Bradycardia (40/minute)
19	40	F	Ischemic heart disease hypertension	Hypertension	30 mg./day	4 days	Fall in BP (210/135 to 1[illegible]0/90) and syncopal episode
20	[illegible]0	F	Diabetes mellitus, hypertension, ischemic heart disease	Angina	[illegible]0 mg/day	Hours	Fall in BP (180/110 to 1[illegible]0/50) and syncopal episode
21	36	M	Ischemic heart disease, ventricular irritability	Arrhythmia	20 mg/day	Hours	Bradycardia (45-50/minute)
22	51	F	Rheumatic heart disease atrial fibrillation congestive heart failure	Arrhythmia	60 mg/day	9 days	Hypotension (84/60)
23	69	F	Hypertension diabetes mellitus, ischemic heart disease obstructive pulmonary disease	Arrhythmia	1 mg IV (one dose)	Immediate	2 1 heart block
24	52	F	Diabetes mellitus, ischemic heart disease	Angina	30 mg/day	1 day	Nausea, headache, drowsiness, and diaphoresis
25	69	F	Hypertension, ischemic heart disease hiatus hernia	Angina	40 mg/day	3 days	Epigastric pain

oral administration of propranolol the adverse reaction rate was independent of the dose Two of six patients who received the drug intravenously had adverse reactions both suffering impairment of atrioventricular conduction and heart block

Discussion

In this study interpretations of untoward clinical events as adverse reactions to propranolol were made by numerous physicians in several hospitals Rarely could the causal role of the drug be established conclusively Nevertheless these findings suggest that the use of propranolol in hospitalized patients is associated with appreciable risks Nine per cent of patients exposed to the drug were judged to have experienced adverse reactions

While no deaths were directly attributed to propranolol nearly one third (8 of 25) of adverse reactions were considered life

Table III Non life threatening reactions to propranolol

Case no	Age (yrs)	Sex	Diagnoses	Indication for propranolol	Dosage	Time from initiation of therapy to onset of toxicity	Description of event
9	65	F	Ischemic heart disease diabetes mellitus, hypertension	Hypertension	3-0 mg/day	4 days	While washing hands patient complained of headache then had syncopal episode
10.	70	F	Ischemic heart disease hypertension PAT	Arrhythmia	30 mg/day	2 days	Found to be excessively drowsy and sleepy Symptoms disappeared when drug was discontinued
11	4	M	Chronic glomerulonephritis hypertension	Hypertension	-40 mg/day	Hours	Intermittent lightheadedness and dizziness concurrent with beginning therapy
12	75	F	Ischemic heart disease acute MI	Angina	60 mg/day	4 days	Bradycardia (40-50/minute)
13	57	M	Ischemic heart disease acute MI	Arrhythmia	40 mg/day	4 days	Gained 5½ lbs. due to fluid retention
14	58	F	Diabetes mellitus, ischemic heart disease acute MI	Angina	30 mg/day	3 days	Blurring of vision
15	55	M	Hypertension	Hypertension	?00 mg/day	21 days	Bradycardia (45/minute)
16	55	M	Ischemic heart disease	Angina	160 mg/day	9 days	Bradycardia (< 60/minute)
17	15	M	Cardiomyopathy PAT	Arrhythmia	120 mg/day	5 days	Hypotension (70/4.)
18.	63	M	Recurrent PAT	Arrhythmia	30 mg/day	Hours	Bradycardia (40/minute)
19	40	F	Ischemic heart disease hypertension	Hypertension	30 mg/day	4 days	Fall in BP (10/135 to 1-0/90) and syncopal episode
0	0	F	Diabetes mellitus, hypertension ischemic heart disease	Angina	30 mg/day	Hours	Fall in BP (180/110 to 1?0/-0) and syncopal episode
21	36	M	Ischemic heart disease ventricular irritability	Arrhythmia	20 mg/day	Hours	Bradycardia (45-50/minute)
??	51	F	Rheumatic heart disease atrial fibrillation congestive heart failure	Arrhythmia	60 mg/day	9 days	Hypotension (84/60)
23	69	F	Hypertension diabetes mellitus, ischemic heart disease obstructive pulmonary disease	Arrhythmia	1 mg IV (one dose)	Immediate	2 1 heart block
4	52	F	Diabetes mellitus, ischemic heart disease	Angina	30 mg/day	1 day	Nausea, headache drowsiness, and diaphoresis
-5	69	F	Hypertension ischemic heart disease hiatus hernia	Angina	40 mg/day	3 days	Epigastric pain

oral administration of propranolol the adverse reaction rate was independent of the dose Two of six patients who received the drug intravenously had adverse reactions both suffering impairment of atrioventricular conduction and heart block

Discussion

In this study interpretations of untoward clinical events as adverse reactions to [illegible] were made by numerous physicians in several hospitals Rarely could the causal role of the drug be established conclusively Nevertheless these findings suggest that the use of propranolol in hospitalized patients is associated with appreciable risks Nine per cent of patients exposed to the drug were judged to have experienced adverse reactions

While no deaths were directly attributed to propranolol nearly one third (8 of 25) of adverse reactions were considered life

Table II Life threatening reactions to propranolol

Case no	Age (yrs)	Sex	Diagnoses	Indication for propranolol	Dosage	Time from initiation of therapy to onset of toxicity	Description of event
1	70	F	Thyrotoxicosis atrial tachycardia	Arrhythmia	1?0 mg/day	5 days	Patient was found confused diaphoretic hypotensive, in slow atrial fibrillation with rate of 30–40/minute
2	77	M	Ischemic heart disease congestive heart failure, ventricular irritability	Arrhythmia	30 mg/day	3 days	Developed acute pulmonary edema requiring morphine furosemide hydrocortisone Nine days later propranolol was reinstituted with immediate recurrence of pulmonary edema
3	58	M	Ischemic heart disease acute MI	Angina	30 mg/day	9 days	Acute pulmonary edema
4	39	M	Ischemic heart disease	Angina	10 mg (two doses)	Hours	One hour after second 10 mg dose patient developed chest pain hypotension sinus bradycardia shock
5	65	M	Hypertension diabetes mellitus ischemic heart disease ventricular irritability	Arrhythmia	30 mg/day	2 days	Acute pulmonary edema
6	55	F	Ischemic heart disease atrial flutter	Arrhythmia	?0 mg (one dose)	2 hours	Two hours after a single dose (?0 mg po) patient developed hypotension (?0/0) cyanosis, and shock
7	76	F	Ischemic heart disease acute MI	Arrhythmia	1 mg IV (one dose)	Immediate	After single IV doses of digoxin (.75 mg) and propranolol (1 mg) immediately developed complete heart block with slow ventricular rhythm and clinical shock
8	79	F	Ischemic heart disease	Arrhythmia	10 mg (two doses)	Immediate	Bradycardia (40-60/minute) and angina shortly after the second 10 mg dose of propranolol

days after propranolol was begun Following nine days without the drug the patient again received propranolol and immediately developed pulmonary edema

Fifteen other non life threatening reactions to propranolol occurred and are detailed in Table III Asymptomatic bradycardia occurred 5 times In five other patients hypotension was noted, this was asymptomatic twice and associated with syncope three times In 4 cases adverse effects involved the central nervous system these included drowsiness, fatigue light headedness, dizziness, headache nausea, or blurring of vision Second degree heart block, epigastric pain, and fluid retention each occurred once

Although adverse reactions became more common with increasing age this trend did not reach statistical significance (Table IV) Reactions were significantly more common in azotemic patients (Table IV) The frequency of adverse reactions also increased significantly with the duration of hospitalization (Table IV)

A number of other factors were evaluated to determine their possible association with adverse reactions These included sex hospital, diagnosis indication for propranolol and concurrent administration of any of the previously mentioned groups of cardiovascular agents None of these factors significantly influenced the frequency of adverse reactions to propranolol

Finally, dosage and route of administration were considered (T[illegible] During

neurotoxic manifestation occasionally reported Hypoglycemia and bronchospasm are potential adverse effects which were not noted in this series

The frequency of adverse reactions to propranolol was almost identical in patients receiving 100 mg per day or more and in those taking less Seven of eight life threatening reactions occurred in patients receiving 30 mg per day or less Equally striking is the rapidity with which many of the adverse reactions developed Nine of the 25 toxic reactions including four of the eight life threatening events occurred within a few hours after drug therapy was initiated These findings may reflect the fact that effective beta adrenergic blockade develops rapidly even after 10 to 20 mg doses of propranolol They suggest that adverse hemodynamic reactions during propranolol therapy are not caused by unusually intensive beta adrenergic blockade or by a direct dose related cardiodepressive action of the drug but rather by the inability of certain patients to tolerate the usual decrease in sympathetic stimulation of the myocardium

In patients with azotemia toxicity occurred more frequently than in those with normal renal function In addition the adverse reaction rate in patients sixty years of age or older was higher than in those who were younger The increase of toxicity with azotemia could be partly caused by impaired renal excretion of active metabolites of propranolol [21] The increase with age might be related to impaired drug metabolizing capacity in the elderly [22] However both relationships could also reflect the increased hazard of toxicity in patients with more severe underlying disease The incidence and severity of cardiac disease may be expected to increase with age This explanation is also suggested by the further observation that patients with long hospitalizations which presumably reflect relatively serious illnesses develop propranolol toxicity far more often than those with short hospitalizations

Summary

Of 13 349 hospitalized medical patients monitored in a drug surveillance program 268 (2 0 per cent) received propranolol during one or more hospitalizations Angina and cardiac arrhythmias were the most common indications for therapy Adverse reactions attributed to propranolol were reported in 25 patients (9 3 per cent) Eight reactions were considered life threatening (pulmonary edema shock complete heart block), all of these involved depressed myocardial function, seven occurred in patients receiving 30 mg per day or less and four occurred within four hours after propranolol was first administered Adverse reactions were more frequent in elderly patients in those with azotemia or long hospital stays and after intravenous administration Propranolol dosage did not influence the frequency of adverse reactions The findings suggest that in some patients serious adverse reactions occur rapidly even after small doses of propranolol and that patients with more severe underlying disease may be predisposed to adverse reactions

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Table IV Propranolol toxicity in relation to age, renal function, and length of hospitalization

	Number of patients	*Number with adverse reaction*	*%*
*Age**			
Less than 50 years	90	5	5 6
50 to 59 years	81	8	9 9
60 years or older	97	12	12 4
*Admission BUN value**			
Less than 25 mg /100 ml	200	13	6 5
25 mg /100 ml or greater	63	12	19 0
*Length of hospitalization****			
Less than 10 days	88	4	4 5
10 to 19 days	124	10	8 1
20 days or more	56	11	19 6

*χ^2 (2 d f) = 2 47 p > 2
**χ^2 (1 d f) = 8 77 p < 01
***χ^2 (2 d f) = 9 66 p < 01

Table V Propranolol toxicity in relation to dosage and route of administration

	Number of patients	*Number with adverse reaction*	*%*
Maximum daily oral dose			
Less than 100 mg	207	18	8 7
100 mg or greater	58	5	8 8
Intravenous (any dose)	6	2	33 3
Total	271*	25	

*Three patients received both oral and intravenous propranolol

threatening In each of these cases the adverse reaction was related to cardiac depression manifested as slowing of heart rate, impaired A V conduction congestive heart failure or hypotension Previous reports have also stressed that serious adverse reactions to propranolol usually consist of these manifestations of cardiac depression[2,4,17] which result from the drug s beta adrenergic blocking activity in patients whose cardiac function is dependent upon adrenergic stimulation

Of seventeen other reactions to propranolol which were less serious in nature eleven also involved cardiac depression (hypotension, bradycardia, or heart block) Four adverse reactions were classified as neurologic Increasing attention has recently been focused upon the psychotropic and psychotoxic effects of beta adrenergic blockers[18] While reduced cardiac output may be responsible for the non specific symptoms of drowsiness lassitude fatigue headache or dizziness (as in Cases 10, 11, and 24) there is some evidence that propranolol and related drugs may produce neuropsychiatric effects unrelated to peripheral beta blockade[18] Central sedative and anticonvulsant properties have been observed in animals Prolonged high dose propranolol therapy in humans has been thought to cause depression leading to suicidal attempts in a few cases[19] Insomnia nightmares, hallucinations and toxic psychoses have also been reported[17,18,20] Visual impairment (Case 14) is another probable

Experimental and laboratory reports

The relationship of coronary collateral inlet flow and retrograde flow in mongrel dogs

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The flow collected from a coronary artery opened to atmospheric pressure distal to its ligation (i.e., retrograde flow) was introduced by Anrep and Hausler[1] as a means to evaluate the intercoronary collateral system in the open-chest animal. Subsequently Gregg and associates[2] popularized the retrograde flow technique as a quantitative tool for assessing the magnitude of the intercoronary collateral system and over the last three decades the bulk of information regarding the collateral network has been uncovered with this technique. Prinzmetal and associates[3] employed radioactive microsphere and erythrocyte myocardial distribution techniques to estimate the actual collateral flow delivered to the peripheral vascular bed of an occluded coronary vessel (abrupt closure) and concluded that retrograde flow underestimated the actual collateral flow. Eckstein[4] stated that retrograde flow exceeds actual collateral flow by 10 per cent in normal dogs. This opinion was later supported by Kattus and Gregg,[5] with the reasoning that more blood would be likely to flow through the intercoronary anastomoses and out a low resistance coronary cannula opened to atmospheric pressure than through the myocardial arterioles, capillaries, and veins of the ischemic myocardium. Levy, Imperial, and Zieske[6] have suggested that retrograde flow is only 30 per cent of actual collateral flow on the basis of regional rubidium 86 myocardial clearance studies. Bloor and Roberts[7] proposed that the intravascular content of isotope is responsible for falsely high myocardial rubidium 86 uptake rates (index of flow) and accounts for the disparity between the results of the retrograde flow and rubidium 86 clearance measurements. In theory the krypton 85 or xenon 133 clearance techniques[8] for measuring myocardial flow are independent of the intravascular isotope content. In normal dogs these techniques estimate collateral flow to be approximately 25 per cent of normal (direct) perfusion rates, whereas retrograde flow measurements in these animals are equivalent to 10 per cent of normal (direct) perfusion rates.[9]

Thus the relationship of retrograde flow to actual collateral flow in the mongrel dog remains controversial. In this study work was undertaken to investigate the relationship between retrograde and actual collateral flow in normal dogs and dogs subjected to chronic myocardial ischemia

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with a large bore cannula for coupling to a constant pressure reservoir of easily ad justable height. The reservoir was em ployed to maintain the systemic pressure in experiments in which acute myocardial ischemia was induced Following major surgical manipulations and prior to the insertion of all catheters heparin (10 mg per kilogram of body weight) was given intravenously followed by repetitive doses of 2 mg per kilogram of body weight every 30 minutes

Retrograde flow measurements The cir cumflex arterial cannula was opened to atmospheric pressure (Fig 1 clamp *B* open clamp *A* fastened) and retrograde flow (RF) collected in a volumetric flask for 20 to 30 seconds and concomitantly re corded with the circumflex cannula flow probe In chronic preparations with large retrograde flows the pressure gradient across the circumflex cannula was estimated (e g predetermined circumflex cannula re sistance X retrograde flow [flow probe]) and counterbalanced by adjusting the height of the retrograde flow outlet tubing to assure atmospheric to subatmospheric pressures at the arterial end of the cannula

Regional myocardial flow measurements Regional myocardial blood flow in the cir cumflex (CX) and anterior descending (A D) myocardial territories was de termined with the use of the krypton 85 clearance technique A Chicago Nuclear scintilation detector collimator was posi tioned over the left ventricle A two inch sodium iodide crystal was mounted 20 cm above the 10 cm diameter orifice of the col limator Saline solutions (0 2 to 0 5 c c) of krypton 85 yielding counts of 20 000 to 50 000 per minute were delivered over periods of 5 to 10 seconds to the A D or CX myocardial regions via the modified Gregg cannula or CX arterial cannula re spectively During the period of krypton 85 infusion the CX arterial cannula system was opened to systemic pressure (Fig 1 clamp *A* open clamp *B* fastened) Under these conditions the mean intraepicardial coronary pressures of the circumflex and adjacent coronary arteries are equal (phasic differentials are unavoidable) and the col lateral flow is assumed equal to zero as is the delivery of krypton 85 from one arterial cannula (e g the Gregg cannula) to the adjacent coronary bed (e g the circumflex bed) Direct perfusion of the circumflex bed was maintained for at least 5 seconds following the termination of krypton 85 infusions K and K_x are defined as the time constants of the logarithmic clearance curves describing desaturation of the A D and CX myocardial territories respec tively The time constants were inter preted to represent the flow per unit mass (in cubic centimeters per minute per 100 Gm) of their respective regions and were determined in the following manner (1) The half time (e g $T_{½}$ expressed in minutes) of the linear stable phase of the krypton 85 logarithmic clearance curve was determined $T_{½}$ is the duration of the interval during which the linear stable phase of the logarithmic clearance curve decreases to half of its initial clearance phase intercept value (2) The time con stant (K) was equated to 100 (0 693/$T_{½}$) c c per minute per 100 Gm To avoid in duction of ventricular fibrillation the krypton 85 clearance phase was limited to 2 to 3 minutes in preparations subjected to severe myocardial ischemia (for example following circumflex arterial cannula oc clusion in the normal dog) The initial fast phase[8] of all clearance curves (5 to 10 seconds duration) was graphically elimi nated and the stable linear phase was ac cepted as representative of mean clearance rates determined with infinitely long de saturation curves[10] The following six krypton 85 washout studies were per formed K and K were individually de termined with (1) the CX cannula opened to systemic pressure (2) the CX cannula clamped and (3) the CX cannula opened to atmospheric pressure for the collection of retrograde flow Ten minute recovery periods were allowed between the washout studies

Change of donor coronary inlet flow This method is a resurrection of an expedient employed by Wiggers and Green[11] in 1936 but performed without the limitations imposed by the art of technology existing at that time The method is illustrated in Fig 2 The increase in the inlet flow of the anterior descending artery (ΔF_A) fol lowing occlusion of the circumflex artery is interpreted as the collateral flow deliv ered from the anterior descending artery to

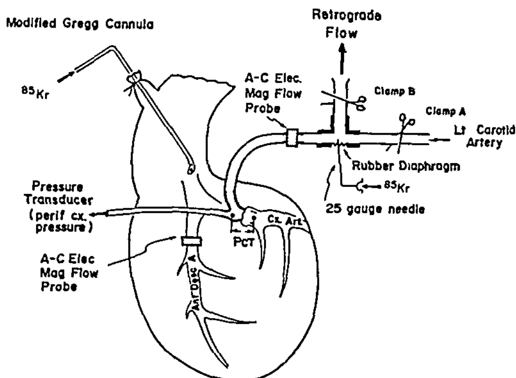


Fig 1 Perfusion of artery *Ant Desc A* Anterior descending artery *Cx Art* circumflex artery P_{CT} catheter pressure gradient

The approach employed was proposed to measure the total anastomotic flow delivered by the normally perfused (donor) coronary arteries to a recipient coronary artery under conditions in which the recipient vessel was either occluded or opened to atmospheric pressure for the collection of retrograde flow The information derived with this approach was supplemented by regional flow determinations in the ischemic and nonischemic myocardial territories under conditions in which a coronary vessel was simply occluded or opened to atmospheric pressure for the collection of retrograde flow In this study the regional myocardial blood flows were obtained with the krypton 85 clearance technique which has been shown in previous reports to provide reasonable estimates of flow under steady state conditions [8]

Methods

The data to be reported were collected in experiments with eight normal mongrel dogs and ten mongrel dogs subjected to chronic myocardial ischemia by placing ameroid constrictors on their proximal circumflex arteries for periods of eight weeks or more prior to study (chronic ischemic preparations) At the time of study, all animals (15 to 35 kilograms in weight) were anesthetized with 30 mg per kilogram of body weight of intravenously administered pentobarbital intubated and ventilated with a Harvard pump respirator The dogs were secured in the right lateral decubitus position and a left thoracotomy was performed The pericardium was incised and sutured to the thoracic wall to minimize movement of the heart The proximal circumflex artery (or the segment of the vessel distal to the ameroid constrictor in the chronic preparation) was dissected ligated proximally, cannulated just distal to the ligature and perfused from the left carotid artery through a series-coupled polyethylene tubing T tube, externally mounted A C electromagnetic flow probe as illustrated in Fig 1 The proximal anterior descending artery was dissected free in order to implant an A C electromagnetic flow probe A small caliber (1 mm internal diameter) modified Gregg cannula was inserted into the left subclavian artery for transient selective catheterization of the left main stem coronary artery The cannula was employed as a conduit for the delivery of saline solutions of krypton 85 to the left main coronary artery The femoral artery was catheterized

Table I Krypton 85 myocardial clearance determinations

	No of determinations	Cx * cannula					
		Opened to systemic pressure		Clamped		Opened to atmospheric pressure	
		K	K_{cx}	K	K	K	K
Normal dogs mean ± S.D † (c c /min /100 Gm.)	8	107 ± 24	110 ± 20	104 ± 22	24 ± 4 5	110 ± 24	13 ± 2 3
Chronic preparations mean ± S D (c c./min /100 Gm)	10	117 ± 19	105 ± 20	112 ± 20	97 ± 16	83 ± 22	21 ± 5 8

K_{ad}, Time constant (c c/min /100 Gm) of the krypton 85 logarithmic clearance curve describing desaturation of the anterior descending myocardium K_{cx}, time constant (c.c./min./100 Gm) of the krypton-85 logarithmic clearance curve describing desaturation of the circumflex myocardium.
†S.D Standard deviation.

scending region Following closure of the circumflex cannula the regional circumflex myocardial flow was 22 per cent ($P < 0.05$) of perfusion rates achieved with direct perfusion of the circumflex cannula under systemic pressure (i e normal perfusion rates) Concomitant with the collection of circumflex arterial retrograde flow the antegrade circumflex myocardial flow was determined to be 12 per cent ($P < 0.05$) of normal perfusion rates

In chronic preparations the anterior descending myocardial flow determinations were not significantly different whether the circumflex arterial cannula was opened to systemic pressure or clamped ($K = 117$ c c per minute per 100 Gm vs $K = 112$ c c. per minute per 100 Gm $P > 0.05$) Following the establishment of retrograde circumflex arterial flow the anterior descending myocardial flow was determined to be 71 per cent of perfusion rates measured when the circumflex arterial cannula was opened to systemic pressure ($P < 0.05$) Following occlusion of the circumflex arterial cannula the collateral flow delivered to the circumflex myocardial region represented 92 per cent of flows achieved through direct perfusion of the circumflex arterial cannula ($P > 0.05$) During the collection of retrograde circumflex arterial flow the antegrade circumflex myocardial flow persisted in magnitudes equivalent to 20 per cent of direct perfusion rates ($P < 0.05$)

During the collection of retrograde circumflex arterial flow alternative routes of krypton 85 circumflex myocardial clearance other than that resulting from effective antegrade flow in the circumflex capillary bed were determined to be insignificant Examples follow (1) The total blood collected retrogradely from the circumflex arterial cannula under anaerobic conditions was placed under the Chicago Nuclear collimator at a level approximated to be that of the central circumflex myocardial mass The radioactivity in all cases (23 determinations) was less than 3 per cent of the detected decrease in radioactivity from the circumflex myocardial region during the collection of retrograde flow The radioactivity of the retrograde flow volumes was determined to be 96 per cent (10 determinations) of an equal volume of systemic blood collected anaerobically during the period in which retrograde flow was collected The krypton 85 content in the retrograde flow blood volumes was thus interpreted to represent krypton 85 delivered transanastomotically from the systemic circulation rather than retrograde circumflex capillary clearance (2) At the termination of the experiment ventricular fibrillation was induced with concomitant occlusion of the anterior descending and circumflex arteries Subsequent to the onset of ventricular fibrillation the systemic pressure was allowed to decrease spon

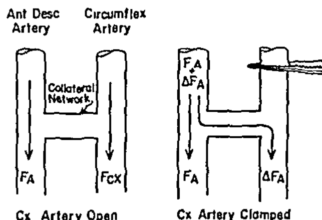


Fig 2 Donor coronary inlet flow method Following occlusion of the circumflex (*Cx*) artery the increase in anterior descending (*Ant Desc*) inflow (ΔF_A) is interpreted as collateral flow delivered from the anterior descending artery to the circumflex myocardial region F_A Antegrade flow to the anterior descending myocardial region F_{cx} antegrade flow to the circumflex myocardial region delivered by direct perfusion of the circumflex artery under systemic pressure

the circumflex myocardial region providing the antegrade capillary flow to the anterior descending myocardial region remains unchanged A similar interpretation is applied to an increase in the right coronary inflow (ΔF_{RC}) following occlusion of the circumflex coronary artery Thus, the total collateral flow (CF) (referred to as collateral inlet flow in subsequent discussions) to the circumflex myocardial region is

$$\text{Collateral flow (CF)} = \Delta F_A + \Delta F_{RC}$$

In this study the right coronary artery was ligated and the total collateral flow was approximated by the collateral flow delivered by the anterior descending artery

In circumstances in which the circumflex artery is opened to atmospheric pressure for the collection of retrograde flow, the increase in flow to the donor coronary vessels is interpreted as total anastomotic flow (AF) delivered by the donor vessels to the collateral system supplying the circumflex artery

The change in donor coronary inflow was measured 15 to 30 seconds following occlusion of the circumflex arterial cannula to allow these determinations to be made under predominantly steady state conditions Compensatory changes in the peripheral bed of the ischemic region are essentially complete within a period of 15 seconds following occlusion of a coronary vessel in normal dogs [12]

The donor coronary inlet flow method assumes that the flow delivered by the donor vessel (e g , anterior descending artery) to its peripheral capillary bed remains unchanged following occlusion of the circumflex arterial cannula or opening the cannula to atmospheric pressure for the collection of retrograde flow The constancy of the anterior descending capillary flow was evaluated by comparing the Krypton 85 clearance rates (K_a) of this region prior to and following (1) circumflex cannula occlusion and (2) the collection of circumflex arterial retrograde flow

Care was taken to employ low resistive circumflex arterial cannulas (e g , 0 05 to 0 1 mm Hg per cubic centimeter per minute resistance) to assure accuracy of the donor coronary inlet flow method For example, antegrade flow delivered from the left carotid artery through a high resistive circumflex cannula reduces the effective pressure head in the peripheral circumflex artery to subsystemic levels Thus anastomotic flow delivered from donor coronary vessels may exist at a time when collateral flow is assumed to be zero (e g , when the inlet end of the circumflex cannula is opened to systemic pressure)

The ECG and systemic pressure were monitored continuously throughout the experiment All pressures and flows were obtained with the use of Statham strain gauge transducers and statham alternating current electromagnetic flow probes respectively and recorded with the Electronics for Medicine recorder

Results

Reported in Table I are the results of the regional anterior descending (K) and circumflex (K_c) myocardial flow determinations obtained with the Krypton 85 clearance technique under the following three conditions (1) the circumflex arterial cannula opened to systemic pressure (2) the circumflex cannula clamped, and (3) the circumflex cannula opened to atmospheric pressure for the collection of retrograde flow

In normal dogs there was no significant difference in the results of the three Krypton 85 washout studies of the anterior de

Table I Krypton 85 myocardial clearance determinations

	No of determinations	CX* cannula					
		Opened to systemic pressure		Clamped		Opened to atmospheric pressure	
		K	K_{cx}	K	K	K	K
Normal dogs mean ± S D† (c c./min /100 Gm)	8	107 ± 24	110 ± 20	104 ± 22	24 ± 4 5	110 ± 24	13 ± 2 3
Chronic preparations mean ± S D (c.c./min /100 Gm)	10	117 ± 19	105 ± 20	112 ± 20	97 ± 16	83 ± 22	21 ± 5 8

K_a Time constant (c.c./min /100 Gm) of the krypton-85 logarithmic clearance curve describing desaturation of the anterior descending myocardium K_{cx} time constant (c.c./min./100 Gm) of the krypton 85 logarithmic clearance curve describing desaturation of the circumflex myocardium.
†S.D Standard deviation.

scending region Following closure of the circumflex cannula the regional circumflex myocardial flow was 22 per cent ($P < 0.05$) of perfusion rates achieved with direct perfusion of the circumflex cannula under systemic pressure (i e normal perfusion rates) Concomitant with the collection of circumflex arterial retrograde flow the antegrade circumflex myocardial flow was determined to be 12 per cent ($P < 0.05$) of normal perfusion rates

In chronic preparations the anterior descending myocardial flow determinations were not significantly different whether the circumflex arterial cannula was opened to systemic pressure or clamped ($K = 117$ c c per minute per 100 Gm vs $K = 112$ c.c per minute per 100 Gm $P > 0.05$) Following the establishment of retrograde circumflex arterial flow the anterior descending myocardial flow was determined to be 71 per cent of perfusion rates measured when the circumflex arterial cannula was opened to systemic pressure ($P < 0.05$) Following occlusion of the circumflex arterial cannula the collateral flow delivered to the circumflex myocardial region represented 92 per cent of flows achieved through direct perfusion of the circumflex arterial cannula ($P > 0.05$) During the collection of retrograde circumflex arterial flow the antegrade circumflex myocardial flow persisted in magnitudes equivalent to 20 per cent of direct perfusion rates ($P < 0.05$)

During the collection of retrograde circumflex arterial flow alternative routes of krypton 85 circumflex myocardial clearance other than that resulting from effective antegrade flow in the circumflex capillary bed were determined to be insignificant Examples follow (1) The total blood collected retrogradely from the circumflex arterial cannula under anaerobic conditions was placed under the Chicago Nuclear collimator at a level approximated to be that of the central circumflex myocardial mass The radioactivity in all cases (23 determinations) was less than 3 per cent of the detected decrease in radioactivity from the circumflex myocardial region during the collection of retrograde flow The radioactivity of the retrograde flow volumes was determined to be 96 per cent (10 determinations) of an equal volume of systemic blood collected anaerobically during the period in which retrograde flow was collected The krypton 85 content in the retrograde flow blood volumes was thus interpreted to represent krypton 85 delivered transanastomotically from the systemic circulation rather than retrograde circumflex capillary clearance (2) At the termination of the experiment ventricular fibrillation was induced with concomitant occlusion of the anterior descending and circumflex arteries Subsequent to the onset of ventricular fibrillation the systemic pressure was allowed to decrease spon

Table II Flow* in normal dogs

Exp No	RF† (c c /min)	CF (c c /min)	AF (c c /min)
1	3 7	5 9	6 5
2	5 0	10 1	11 6
3	1 6	4 1	5 1
4	2 9	7 0	7 8
5	4 0	8 7	9 7
6	4 7	9 3	10 7
7	4 5	9 6	11 1
8	3 2	8 1	9 8
Mean ± S D	3 7 ± 0 9	7 9 ± 1 7	9 0 ± 2 2

*Mean antegrade coronary flows A D 35 2 c c per minute CX art 34 4 c c per minute
†RF Retrograde flow CF increase in anterior descending inflow following circumflex cannula occlusion AF increase in anterior descending inflow following the establishment of circumflex arterial retrograde flow

Table III Flow* in chronic preparations

Exp No	RF (c c /min)	CF (c c /min)	AF (c c /min)
1	65 0	20 5	62 7
2	63 0	15 9	59 5
3	48 0	19 2	45 9
4	91 0	26 6	83 3
5	73 5	18 1	69 4
6	70 0	13 2	65 0
7	90 0	17 9	84 0
8	120 0	21 5	99 6
9	160 0	22 0	128 3
10	86 0	27 0	80 4
Mean ± S D *	86 2 ± 29 7	20 2 ± 3 6	77 8 ± 2 3

*Mean antegrade coronary flows A D = 30 5 c c per minute CX art = 23 0 c c per minute

taneously and krypton 85 clearance from the myocardium was measured to be less than the equivalent of 1 c c per minute per 100 Gm (10 determinations) The clearance was assumed to be a result of evaporation Collimator ventilation was maintained during these determinations

The results of the donor coronary inlet flow and retrograde flow methods are reported for the individual experiments with normal dogs in Table II and the experiments with chronic preparations in Table III The results of the individual experiments represents the mean of three or more determinations

In normal dogs the retrograde flow determinations were 47 per cent ($P < 0.05$) of collateral flows (CF) estimated with the inflow method during closure of the circumflex cannula Retrograde flow measurements were 41 per cent ($P < 0.05$) of anastomotic flows (AF) estimated with the inflow method during the collection of retrograde circumflex arterial flow

In chronic preparations retrograde flow measurements were 420 per cent ($P < 0.05$) of collateral flows (CF) and 111 per cent ($P > 0.05$) of anastomotic flows (AF) determined with the inflow method

In chronic preparations the difference between the retrograde flow measurements and the anastomotic flows (AF) determined with the donor coronary inflow method during the collection of retrograde flow may be accounted for on the basis of the following mechanisms (1) The flow to the

peripheral bed *of the donor* vessel decreased. This was demonstrated with the krypton 85 washout technique, e.g., the *anterior* descending capillary flow decreased to 71 per cent of normal perfusion rates during the collection of retrograde flow (Table I). (2) Measurement of flow to the proximal *anterior descending* vessel does not monitor the potential contributions to anastomotic flow of the more proximal donor vessels. In the dog the primary septal artery is the major potential source of anastomotic flow proximal to the anterior descending artery. The primary septal vessel supplies approximately 10 per cent of the total left ventricular flow in the normal dog.[22] The contribution of the primary septal artery to retrograde flow was estimated in five chronic preparations. In these animals the septal vessel was dissected free and acute closure of this coronary artery branch produced small discrete reductions in retrograde flow as monitored with the circumflex cannula A.C. electromagnetic flow probe. The mean reduction in retrograde flow in these experiments was 4 per cent (range 1 to 7 per cent).

Discussion

In this study the hemodynamics of the coronary peripheral and collateral vascular networks were examined under conditions in which a coronary artery was simply occluded or opened to atmospheric pressure for the collection of retrograde flow. Two methods were employed to investigate the peripheral and collateral circulatory dynamics. The donor coronary inlet flow method was proposed to measure the total anastomotic flow delivered by donor coronary vessels to the coronary collateral system and the krypton 85 clearance technique was utilized to measure the regional anterior descending and circumflex myocardial blood flow.

The validity of the krypton 85 clearance technique depends upon stable flow conditions during the period of measurement. In studies in which the krypton 85 washout method was employed during a two- to three-minute interval following abrupt interception of antegrade circumflex arterial flow, compensatory changes in the distal circumflex bed (e.g., mainly ischemia induced vasodilatation and decreased myocardial contractility) occur most intensely in normal dogs and primarily within the initial 10 to 15 second interval following occlusion of the circumflex cannula. Evidence for this is provided by a typical peak reactive hyperemic flow vs. the duration of circumflex cannula occlusion curve.[17] In chronic preparations with well developed collaterals reactive hyperemic responses of the peripheral circumflex vascular bed were not observed following the release of temporary occlusions (> 1 minute) of the circumflex cannula. Slow changes in local coronary vasoregulation or myocardial contractility over prolonged periods (e.g., hours) were not ruled out. The purpose of this study was to measure the degree of collateral flow delivered to the circumflex bed during the initial two to three minutes following closure of the circumflex artery or the establishment of retrograde flow. In all studies the krypton 85 myocardial washout period was monitored for a minimum of two minutes, thus minimizing errors resulting from early compensatory changes occuring in the distal circumflex bed. During periods of slow changes in flow, the krypton 85 clearance technique provides reasonable estimates of mean flow during the interval of measurement.[9]

The krypton 85 clearance technique was employed in this study primarily to supplement rather than to compare the information derived with the donor coronary inflow method. For example, the validity of the inflow method is entirely dependent upon stable flows within the peripheral donor coronary beds during periods in which the adjacent recipient myocardial region is subjected to ischemia. It was shown with the krypton 85 washout studies that the capillary flow of the anterior descending (donor) artery does not change significantly under conditions in which the circumflex cannula is clamped or opened to atmospheric pressure with the exception of the chronic preparation following the establishment of retrograde flow. In the chronic preparation the antegrade anterior descending flow decreased to 71 per cent of normal *perfusion* rates during the collection of retrograde circumflex arterial flow (to be discussed in a following section).

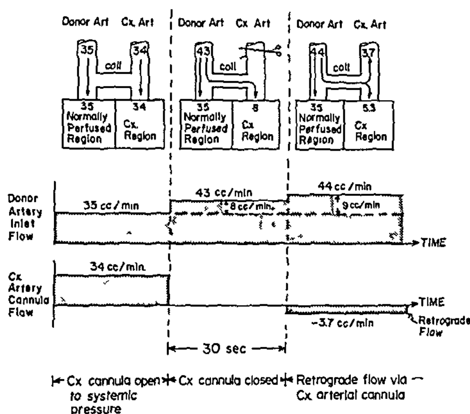


Fig. 3. Circulatory dynamics. *Upper drawing:* Schematic representing the distribution of the donor coronary (e.g., anterior descending) inlet flow of normal dogs under conditions in which the circumflex arterial cannula is (1) open to systemic pressure, (2) clamped, and (3) opened to atmospheric pressure for the collection of retrograde flow. The numerals depicted in the upper drawing represent the mean flows (cubic centimeters per minute) reported for normal dogs in Table II. The *middle* and *lower drawings* represent the donor coronary and circumflex arterial flows (cubic centimeters per minute), respectively, under the three conditions described above.

The krypton 85 washout technique yields estimates of the flow per unit mass of the myocardial region under study. Thus the donor coronary inflow and krypton 85 washout techniques are not comparable on a flow to flow basis unless the mass of the region under study is known. For this report it was chosen to compare these methods by normalizing collateral flow measurements to the normal perfusion rates (all flows are reported in Tables I to III). For example, in the normal dog the circumflex myocardial collateral flow during closure of the circumflex artery was estimated to be 23 per cent of normal perfusion rates with the inflow method and 22 per cent of normal perfusion rates with the washout technique. The difference was not significant. In chronic preparations the collateral flow was estimated to be 88 and 92 per cent of normal perfusion rates with the inflow and washout techniques, respectively. Again the difference between the two methods was not significant.

Fig. 3 is presented to provide a schematic of the peripheral and collateral circulatory dynamics which summarize the combined results of the donor coronary inlet flow and krypton 85 clearance studies in normal dogs. Illustrated in the upper portion of Fig. 3 is the distribution of the donor coronary inlet flow of normal dogs (mean values are presented) under conditions in which the circumflex arterial cannula is (1) open to systemic pressure, (2) clamped, and (3) open to atmospheric pressure for the collection of retrograde flow. Following occlusion of the circumflex arterial cannula the mean donor coronary inlet flow increased from 35 to 43 c.c. per minute. The results of the krypton 85 clearance studies (Table I) indicate that the antegrade flow to the peripheral bed of the anterior descending artery was not significantly changed following occlusion of the circumflex arterial cannula. Therefore the increase in the donor coronary inlet flow (e.g., 8 c.c. per minute) is interpreted as

collateral flow delivered to the peripheral vascular bed of the occluded circumflex artery Following the establishment of retrograde circumflex arterial flow the donor coronary inlet flow increased to 44 c c per minute Again utilizing the krypton 85 clearance technique the peripheral flow of the anterior descending artery was determined to be virtually unchanged following the establishment of retrograde flow (Table I) Therefore the increase in the donor coronary inlet flow (9 c c per minute) is interpreted as the total anastomotic flow delivered to the collateral system during the collection of retrograde flow *Of the total transanastomotic flow (9 c c per minute)* delivered to the recipient circumflex vascular bed 3 7 c c per minute are diverted retrogradely via the circumflex arterial cannula The difference between the total anastomotic flow (9 c c per minute) and retrograde flow (3 7 c c per minute) equals 5 3 c c per minute and is interpreted as anastomotic flow delivered antegradely to the peripheral bed of the circumflex artery The presence of an effective antegrade capillary perfusion of the circumflex myocardial region concomitant with the collection of retrograde circumflex arterial flow was demonstrated with krypton 85 washout studies (Table I)

In chronic preparations the flow to the peripheral bed of the anterior descending vessel determined with the krypton 85 washout method was not significantly changed following closure of the circumflex arterial cannula Thus the increase in total donor coronary inlet flow following occlusion of the circumflex arterial cannula would reasonably *be interpreted as* collateral flow delivered to the recipient circumflex myocardial region Following the establishment of retrograde circumflex arterial flow the flow to the peripheral bed of the *anterior descending* artery was reduced to 71 per cent of levels achieved during direct perfusion of the circumflex arterial cannula This decreased peripheral anterior descending flow is presumably a reflection of *the decreased* effective perfusion pressure throughout the anterior descending epicardial network resulting from the large increase in anastomotic flow established in this bed during the collection of circumflex arterial retrograde flow Upon re establishment of antegrade circumflex arterial flow a marked reactive hyperemic response was noted in the circumflex arterial system and a mild reactive hyperemic response was observed in the anterior descending inlet flow The mild reactive hyperemic response of the anterior descending inflow may be the result of one or two mechanisms For example (1) hypoxia induced within the anterior descending bed as a result of the reduced capillary flow (i e 71 per cent of normal) during the collection of retrograde flow and (2) a reflection of the reactive hyperemic *response* in the circumflex bed *The latter mechanism* is explained on the basis of the marked reactive hyperemic circumflex arterial inflows and the resultant pressure gradients generated across the circumflex cannula arterial and arteriolar systems The reduced intra arterial pressures of the circumflex bed could thus establish transient transanastomotic pressure gradients and collateral flows temporally related to the circumflex arterial hyperemic response

The continued perfusion of the circumflex myocardial region following the establishment of circumflex arterial retrograde flow is not unexpected since a spatial intravascular pressure gradient must exist throughout the circumflex myocardial region falling from near systemic pressures at the collateral inlets to atmospheric pressures *in the central epicardial* portions of the circumflex arterial network Thus an effective perfusion pressure is maintained for the subepicardial collateral complexes in both normal and chronic ischemic dogs *during the collection of retrograde flow* In nchroic preparations retrograde flow collected in the conventional manner by maintaining the circumflex arterial cannula at atmospheric pressure does not reduce the pressures in the entire circumflex epicardial bed to atmospheric levels During the collection of retrograde flow in systems with large epicardial anastomoses an intra arterial epicardial pressure gradient must necessarily be established from the normally perfused coronary arteries to the circumflex arterial cannula Thus the tributaries arising from at least the peripheral portions of the circumflex artery continue to receive some degree of perfusion

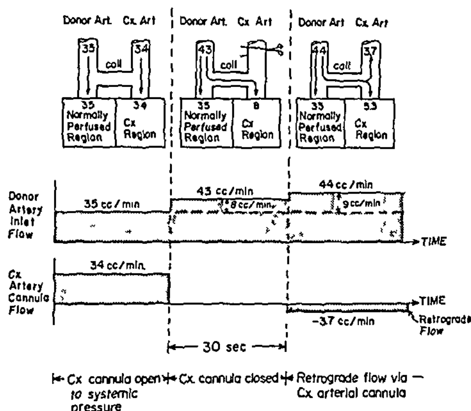


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Determination of systolic intervals utilizing the carotid first derivative

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Left ventricular ejection time (LVET) is an important parameter of cardiac performance, reflecting both the heart's muscle and pump functions. In one prospective blind study of unselected hospitalized patients[1] an abnormally low LVET when corrected for heart rate reliably distinguished 80 per cent of those with manifest heart disease, while only 12 per cent of patients had abnormal LVET without having any manifest cardiac malfunction. This and other studies[2,3] have shown that LVET can be used both as a reflection of functional status and as a practical screening procedure for detecting cardiac abnormality.

It has now become a standard procedure in measuring the LVET and the other systolic intervals to employ the externally recorded carotid sphygmogram. Various studies[4,5] have proved that LVET so obtained is accurate and differs negligibly from those directly taken from the central aortic curve. However, a number of technical difficulties may be encountered during the procedure of external recording of the carotid pulse. A particularly restless and uncooperative individual or persons with obesity and respiratory problems may preclude obtaining a technically good carotid tracing despite manual expertise. Even in a cooperative patient tremors and other body movements as well as respiratory excursions may distort the base line and introduce artifacts into the carotid tracing (Fig. 1). Also during exercise maintaining a stable base line of the recording may be difficult. Finally, sometimes, as in aortic valvular disease, the standard points of measurement—the carotid upstroke (CAR_U) and incisura (CAR_I)—are poorly defined even without base line or other low frequency artifacts. (This will equally invalidate the other systolic intervals.)

To obviate the above difficulties, we attempted to measure the systolic intervals incorporating the first derivative of the carotid displacement pulse (dD/dt)[6]—i.e., the velocity tracing—and compare them with those obtained utilizing the carotid pulse itself. The dD/dt, expressing the rate of change of the carotid displacement curve with respect to time, is analogous to the rate of rise and fall of arterial pressure expressed as its first time derivative.[6]

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during the collection of retrograde flow. Fulton[13] has demonstrated, with his stereoradiographic technique, large subendocardial collateral complexes which could provide a source of antegrade capillary flow not easily diverted by opening the circumflex arterial cannula to atmospheric pressure.

The combined results of the donor coronary inflow and krypton 85 clearance studies are summarized as follows: (1) retrograde flow was 47 per cent of actual collateral flow in normal dogs; (2) retrograde flow was 420 per cent of actual collateral flow in chronic preparations, reflecting the results of opening the circumflex arterial system supplied by large caliber anastomoses to atmospheric pressure; and (3) concomitant with the collection of retrograde circumflex arterial flow, antegrade flow to the ischemic circumflex myocardium persists in both normal dogs (13 per cent of normal perfusion rates) and chronic preparations (20 per cent of normal perfusion rates).

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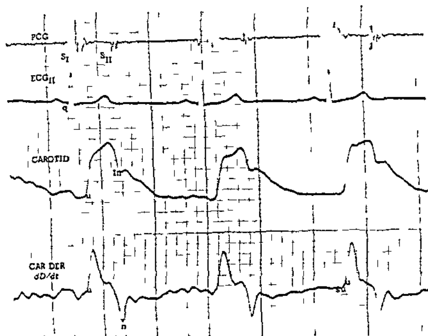


Fig 2 Top to bottom phonocardiogram (PCG) ECG Lead II carotid displacement pulse (*CAROTID*) and its first time derivative pulse (*CAR DER dD/dt*) S_I = First heart sound S_{II} = second heart sound *u* = upstroke *In* = incisura *su* = slow upstroke *n* = nadir Note constancy of *u* and variability of *su*

II From carotid CAR_I II_A

PRE EJECTION PERIODS

1 From derivative (q DER) *minus* PTT from derivative

II From carotid (q CAR) *minus* PTT from carotid

Preliminary investigation

Definition of points in the derivative

Upstroke points In the derivative trace the initial upstroke is normally slow and not always well defined when the inscription of the base line is thick or irregular But the rapid upstroke i e the change of thick to thin portion of the derivative upstroke tends to be sharp and well delineated (Fig 2) On closer inspection of the simultaneously recorded indirect carotid pulse and its first derivative it was noted that the rapid upstrokes in both the tracings were virtually simultaneous whereas the slow up stroke of the derivative was a very much earlier event (Fig 2) We therefore included in this investigation a preliminary study comparing LVET s derived from the slow upstroke using the always sharp nadir of the derivative as the end point vs the carotid derived LVET s Data were collected in a blinded manner as detailed earlier in 20 subjects including 10 with heart disease It was confirmed that the mean value of the rapid upstroke of the derivative as compared to the slow up stroke was much closer to the mean value of the carotid upstroke and that derivative LVET using the rapid upstroke showed closer correlation with the carotid LVET Results of this preliminary study are shown in Table I

Nadir point This remains uniformly sharp and easily identifiable under all situations Thus it serves as a very reliable measuring point when the carotid incisura may be obliterated or blunt (Fig 1) A small but consistent difference in its timing in relation to the carotid incisura has been shown to be statistically insignificant (see below)

Results

The mean values of LVET s and other systolic intervals derived from both the carotid and its derivative traces and the comparison of the results from the two methods are shown in Tables II and III

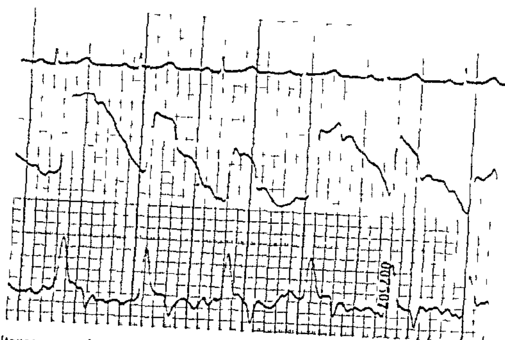


Fig. 1 Simultaneous recording of ECG Lead II, indirect carotid pulse (line 2), and its first time derivative (line 3) in a patient with respiratory disease. The derivative tracing remains steady in spite of fluctuation in the carotid tracing.

Materials and method

Subjects. We studied 53 ambulatory patients, 30 male and 23 female, aged 52 to 69. Thirty were normal subjects of whom 15 were men without clinical or electrocardiographic evidence of any heart disease; the other 23 had documented hypertensive and/or coronary artery disease. These were otherwise unselected individuals drawn from a large screening clinic after exclusion only of those with arrhythmias.

Recordings. With the subjects in the supine position a polygraphic recording was made as follows during relaxed expiratory apnea approximately at the same time of the day: (1) right carotid displacement pulse, using a Schwarzer photoelectric contact sensor; (2) first derivative of the carotid pulse by passing the carotid pulse wave through a RC network differentiator, technical characteristics of which are described elsewhere[9]; (3) ECG Lead II; (4) phonocardiogram at mesoapex using Schwarzer contact microphone. Recording was made on a six channel Schwarzer direct writing recorder model No. 622 at a paper speed of 50 mm. per second with time lines at 20 msec.

Measurements. The same cycles were used for both carotid and its first derivative measurements. With q of ECG as zero time, timing of the following points was measured (Fig. 2): onset of the rapid carotid upstroke (CAR_u), the carotid incisura (CAR_{In}), onset of the aortic component of the second heart sound (II_A), onset of the rapid upstroke of the first derivative (DER_u), and nadir of the derivative (DER).

Blinding procedure. To avoid conscious bias, measurements were made separately for the carotid and its derivative without knowledge of results obtained from the other pulse output. In each case five consecutive cardiac complexes were measured in milliseconds to a precision of 5 msec and averaged. Calculations of actual systolic intervals were made only at the end when the timings of all the above points had been measured and averaged, thus avoiding any unconscious bias.

Calculations. The following intervals were calculated from the measurements:

LEFT VENTRICULAR EJECTION TIME (LVET)

I. From derivative

(a) Slow upstroke to nadir: DER_{su}–DER (used only in preliminary study)

(b) Rapid upstroke to nadir: DER–DER

II. From carotid

Upstroke to incisura: (CAR_u–CAR_I)

PULSE TRANSMISSION TIME (PTT)

I. From derivative: DER_u–II_A

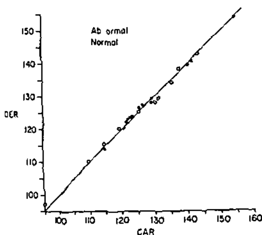


Fig 3 Relationship between the rapid upstroke points of carotid (*CAR*) and its derivative (*DER*) Statistical data in text and tables Units in milliseconds

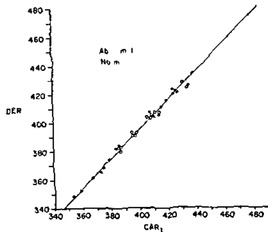


Fig 4 Relationship between the carotid incisura (CAR_I) and the derivative nadir (*DER*) points Statistical data in text and tables Units in milliseconds

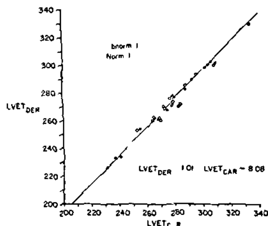


Fig 5 Relationship between two groups of LVET's derived from the carotid ($LVET_{CAR}$) and its derivative ($LVET_{DER}$) pulse The regression equation is derived from the difference of slope and intercept values of the two LVET's Units in milliseconds

(Rate corrections were unnecessary since measurements by each method were made in the identical cycles) The numerical values in the normal and abnormal groups were combined for final analysis to embrace larger variation and heterogeneity in clinical material

The main difference between the two upstroke points (CAR DER$_u$) was only 1 1 msec (Fig 3) which was statistically insignificant ($P > 0.5$) Thus the rapid upstrokes in both tracings may be considered to start simultaneously This appears to be a function of the response of the RC differentiator

The difference between the two terminal points (CAR_I DER) was also small (Fig 4) the DER being 5 6 msec earlier ($P > 0.2$) Thus the LVET was statistically identical in both cases (Fig 5) the mean difference in the derivative tracing being only 4 4 *msec shorter* ($P > 0.2$)

The mean difference in PEP obtained from the two tracings was small (4 3 msec) and not significant ($P > 0.05$) The slightly higher PEP in the derivative trace was mainly due to the shorter PTT

PTT was significantly shorter in the derivative tracing (mean 5 5 *msec* $P < 0.001$) owing to the slight but consistently early inscription (Fig 4) of the nadir point

Discussion

In the recent years increasing attention has been paid to the development of simple and more accurate noninvasive methods for determination of systolic time intervals The apexcardiogram and its first derivative [7] ear densitogram[8] and its first derivative [9] have all been described in these efforts The first derivative of the carotid pulse reveals points of slope change that are often not apparent or blurred in the original curve and may thus serve as an alternate and easier noninvasive technique for this purpose

Our results indicate that the systolic time intervals determined by utilizing the point of the carotid first derivative curve

*Table I Preliminary study—LVET**

	Mean	SD	SE
I *Derivative*			
q DER	111 6	15 41	3 45
q DER	400 2	28 79	3 95
LVET	288 6	23 35	5 22
II *Carotid*			
q CAR	127 3	14 38	3 22
q CARI	404 9	28 69	6 42
LVET	277 6	24 36	5 45

	r	b	a	t	P
Carotid vs derivative					
Upstroke points	0 85	0 91	−4 32	3 33	$P < 0\ 005$
Incisura or nadir point	0 99	1 01	−10 92	1 01	NS†
LVET	0 95	0 91	35 77	1 44	NS

*Measurement (msec) by slow upstroke (DER) and nadir (DER) of carotid first derivative and comparison with those by carotid pulse 20 subjects
†Not significant

*Table II Systolic intervals**

	Mean	SD	SE
q II_A	479 2	28 09	3 86
Carotid			
q CAR	126 8	13 44	1 85
q CARI	405 8	28 13	3 86
LVET	279 0	24 20	3 32
PTT	76 6	6 71	0 92
PEP	100 3	12 59	1 73
Derivative			
q DER_u	125 7	13 20	1 81
q DER	400 2	28 79	3 95
LVET	274 6	24 76	3 40
PTT	21 1	7 48	1 03
PEP	104 6	11 62	1 60

*Measurements (msec) by rapid upstroke (CAR) and incisura (CARI) of carotid pulse and rapid upstroke (DER) and nadir (DER) of carotid first derivative 53 subjects

Table III Comparison of systolic intervals obtained from carotid pulse and its first derivative

	r	b	a	t	P
1 Upstroke points	0 98	0 96	3 63	0 47	NS
2 Terminal points (incisura or nadir)	0 99	1 01	−10 92	1 01	NS
3 LVETs	0 99	1 01	−8 08	0 92	NS
4 PEPs	0 95	0 87	16 03	1 82	NS
5 PTTs	0 82	0 91	−3 23	3 98	$P < 0\ 001$

*Not significant

Transient S-T elevation detected by 24-hour ECG monitoring during normal daily activity

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The detection of transient S T elevation and its interpretation poses a difficult problem That this condition has clinical significance was stressed by Prinzmetal[1] in his description of variant angina pectoris Until recently cases with documented S T elevation were found to have this feature mainly by chance because their ECG at rest and on exercise are usually normal[2] The finding of transient S T elevation during exercise in patients after myocardial infarction has been described by using radio telemetry[3] The continuous around the clock recording of the ECG by the Holter system[4] enables the examinee to carry his normal daily routine during the monitoring and recently sporadic cases with transient S T elevation have been described using this method[5-7]

In this study patients in whom transient S T elevation was found by continuous ambulatory monitoring are presented their clinical background is described and the possible significance of this finding in each case is discussed

Material and methods

The 7 patients described here were among 174 patients who were referred to us with atypical chest pain and/or palpitations for 24 hour ECG monitoring A conventional 12 lead ECG was performed on all patients while a single Master step test and multi stage bicycle ergometric examination was performed when indicated The Holter* tape recording system was used with the model E Electrocardiocorder which has an improved low frequency response Three non polarizable silver silver chloride electrodes (Mannen Creatbach) were used The exploring electrode was placed over the V_5 position The negative electrode was placed in the fourth intercostal space at the right sternal border and the ground electrode was placed at the manubrium sterni The complex obtained closely resembled Lead V_5 of the conventional ECG The tapes were screened for possible ECG abnormalities on the Electrocardioscanner and the suspicious segments seen on the screen were printed out on regular ECG paper

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correlated very well with those obtained using the carotid displacement pulse itself both in normal subjects and in those with heart disease. There was no statistically significant difference between the mean values of ejection times obtained by either method. This remained true whether the ejection time is calculated from the slow upstroke or the rapid upstroke points of the first derivative, although the LVET derived from the latter point correlated more closely (i.e., slope value nearer to 1 and intercept closer to 0) with the carotid LVET.

Both the upstroke and nadir points in the derivative curve were earlier than those in the carotid tracing. This was not entirely unanticipated, since there is some phase shift to be expected in the derivative due to the equivalent of a shorter time constant as a characteristic of the RC network differentiator. That the points in the time derivative trace appeared to be more reliable is also understandable, since both the rapid carotid upstroke and the incisura ideally represent the points of change of slope and these may be poorly defined in carotid curves owing to technical factors and low frequency artifacts which do not appear in time derivative curves.

The consistently early inscription of the derivative nadir with respect to the carotid incisura may be fortuitous. Normally the incisura of the central aortic pulse is registered with a slight delay after the actual aortic valve closure, perhaps due to the continued small forward flow during early left ventricular relaxation. Kumar and Luisada[10] found this delay to be around 15.6 msec. In this study the nadir of the derivative, in relation to the carotid incisura, has been early by an average of 5.6 msec. Thus the derivative nadir may accidentally reflect better than the carotid incisura the time of the actual change of slope of the central pulse and, therefore, a consistent "underestimate" of LVET thus obtained may be really closer to the actual ejection period.

Summary

Left ventricular ejection time (LVET) is a useful parameter of cardiac function which may be difficult to measure in restless, dyspneic, and uncooperative patients. Certain well defined points of the first time derivative of the carotid displacement pulse are suitable to determine LVET and appear more reliable than the corresponding points in the carotid pulse itself under technically adverse situations. Systolic time intervals thus obtained correlate well with those determined by utilizing the undifferentiated carotid pulse wave. Thus the carotid first time derivative (dD/dt) serves as a more versatile and convenient method for such measurements because of greater freedom from motion artifact and better definition of points.

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Reason for monitoring	*Findings during monitoring*	*Diagnosis*
Palpitations	Abrupt changes in rate from 84 to 140 inversion of T waves S-T elevation of 2 mm	Neurocirculatory asthenia suspected
Chest pain	Repeated S-T elevation of 2 mm T wave inversion	Neurocirculatory asthenia
Chest pain dizzy spells	S-T elevation of 2 mm S-T depression of 1 mm supraventricular tachycardia ventricular premature beats	Post myocardial infarction
Chest pain and palpitations	S-T elevation of 1 5 mm S-T depression and T wave inversion atrial premature beats and atrial tachycardia	Post myocardial infarction
Chest pain palpitations syncope	S-T elevation of 2 mm	Post myocardial infarction
Chest pain breathlessness	S-T elevation of 3 4 mm	Variant angina pectoris
Chest pain	S-T elevation of 4 5 mm	Variant angina pectoris

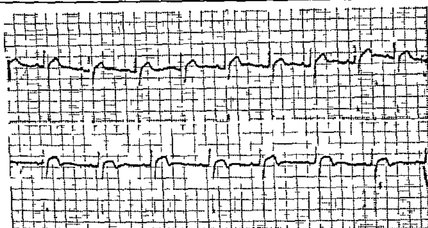


Fig 2 *Upper panel* ECG tracing of patient No 1 as recorded during most of the 24 hour monitoring period *Lower panel* S-T elevation observed during sleep lasting for 5 minutes and not causing him to awake

strip with S T elevation showed QRS complexes identical or closely resembling for direction and amplitude those of the preceding strip without the S T elevation and the amplitude of the QRS closely approximated the amplitude of V_5 in the standard ECG

Results

The seven patients who showed transient S-T elevation on 24 hour monitoring were invariably male and their age varied from 18 to 66 years (Table I)

In view of their clinical background and subsequent ECG findings the patients were divided into three groups

1 *Patients with neurocirculatory asthenia*

CASE 1 B V 18 year old male referred because of palpitations which troubled him at rest and during exercise Physical examination was negative The resting ECG showed a single atrial premature beat A Master test showed no ST T changes but several atrial premature beats were recorded some of which were blocked On ergometric examination[19] at a load of 100 Watts per minute and at a heart rate of 160 per minute inverted T waves in I and flat T waves in aVF were noted The 24 hour monitoring during the day detected sinus tachycardia of 170 per minute when the patient ascended a flight of stairs or performed other relatively light physical effort and this was usually accompanied by T wave inversion S-T elevation of 2 mm was recorded during sleep lasting for 5 minutes and not causing him to awake (Fig 2) A presumptive diagnosis of neurocirculatory asthenia was made in this patient.

Table 1 Details of 7 patients with transient S T elevation detected by continuous 24 hour monitoring

Patient No and initials	Age (yr)	Sex	Resting ECG	Master two step test	Bicycle exercise test
1 B Y	18	M	Normal	Normal	Normal
2 C A	28	M	T wave inversion	T wave inversion more marked	—
3 F C	61	M	Anteroseptal infarction	—	S-T depression of 1 mm V₄ and ventricular premature beats
4 H A	56	M	Anteroseptal infarction	Positive	S T depression of 3 mm in V₄
5 M B	54	M	Anteroseptal infarction	—	—
6 H Y	66	M	Right B B B ventricular premature beats	—	—
7 B Z	47	M	Right B B B	Normal	—

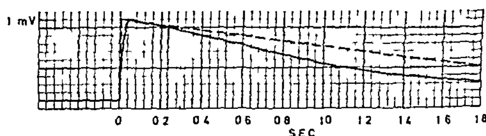


Fig 1 Step voltage decay curve of a Sanborn 100 ECG machine (solid line) and of the Holter Avionics system (interrupted line) It can be seen that after 200 msec both systems have similar decay A 90 per cent decay is reached in the Sanborn 100 machine after 300 msec and in the Holter Avionics system after 240 msec

using an improved method of operation [8] The reliability of the system as to reproduction of S T segment was tested earlier by comparing the tracings of individuals with normal ECG pattern and of others with pathological ST T changes recorded through a conventional ECG machine with that obtained through the Avionics Electrocardiocorder E and its interpreting equipment the results demonstrated identity of the tracings [9] Furthermore the Electrocardiocorder and reproduction system have a correction network for improving its low frequency response which is not a simple RC network Therefore we compared the low frequency response of a conventional ECG machine (Sanborn 100) and the Electrocardiocorder E by applying to both of them a step voltage Fig 1 shows that the step voltage decays to 90 per cent of its original value in the conventional ECG machine after 300 msec and in the Avionics system after 240 msec Since the duration of the S T segment is not longer than 200 msec and after this interval the decay in the step voltage in the Avionics system is similar to that of the conventional ECG (92 per cent and 93 per cent respectively) we conclude that for clinical purposes this system is satisfactory for reproducing the S T segment

The patients were requested to keep a record of their activities and symptoms while being taped so that these could be subsequently correlated with ECG findings

S T elevation was regarded as significant if the following conditions were fulfilled it occurred for at least 12 seconds the ECG strip had a stable isoelectric line (defined as being a straight line drawn through three subsequent T P segments) the S T segment being 1 5 mm or more [illegible] t line the

mental obstruction of 75 per cent in his right main coronary artery We believe that with the development of selective coronary arteriography and bypass surgery the exact diagnosis of a condition with the above mentioned pathological associations and a poor prognosis has special importance Since the history in this syndrome is atypical and both the resting and the exercise ECG are usually normal continuous ECG monitoring under dynamic conditions as described above is of particular assistance in diagnosing these cases

Summary

Seven out of 174 patients subjected to continuous 24 hour ECG monitoring because of atypical chest pain and/or palpitations were found to have transient S T elevation Two were diagnosed as suffering from neurocirculatory asthenia three had myocardial infarction and two suffered most probably from Prinzmetal s variant angina pectoris We believe that the finding of transient S T elevation is of special significance because of the pathological and therapeutic implications and that continuous ECC monitoring during unrestricted daily activities provides a unique *opportunity to detect this condition more* frequently

We are greatly indebted to Prof J Weinmann of the Bioengineering Dept of the Hebrew University–Hadassah Medical School and to Dr Y Mahler of the Electronics Dept of the Hadassah University *Hospital for their useful help The devoted technical assistance of Mrs Batia Glassman is gratefully* acknowledged

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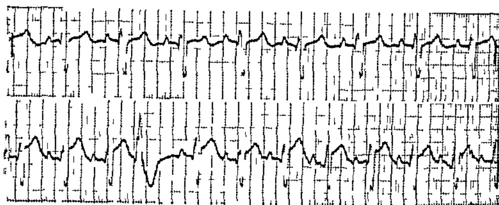


Fig 7 *Upper panel* LCG tracing of patient No 6 as recorded during most of the 24 hour monitoring period *Lower panel* S T elevation recorded during walking accompanied by chest pain

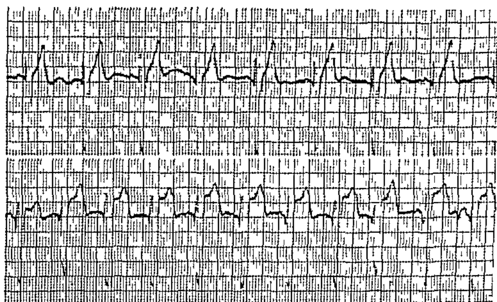


Fig 8 *Upper panel* LCG tracing of patient No 7 as recorded during most of the 24 hour monitoring period *Lower panel* S T elevation recorded during a 7 minute period of chest pain

therapy[12] The detection of S T elevation in the two cases described above suggests the possibility of sympathetic induced coronary artery constriction Since our patients were relatively young we assume that they have normal coronary arteries however that vasospasm in a normal artery can result in S T elevation remains to be proved

The second group of patients consisted of three who had suffered a previous myocardial infarction It is known that acute ischemia in cardiac muscle alongside an infarcted area may give rise to S T elevation[13] and it is thought to explain this finding in the patients of this group

The third group had atypical chest pain and S T elevation at rest or during ordinary physical activity *All* these findings are compatible with the diagnosis of Prinzmetal s variant angina pectoris[1] This condition implies the presence of a high grade localized occlusion in the proximal part of one of the three main coronary arteries Prinzmetal and co workers[1] mention three such cases Peretz and Silverman and Flamm[7] describe one case each who at post mortem examination show severe localized stenosis at the proximal end of one of the three main coronary arteries Macalpin and Kattus[14] performed coronary arteriography on six cases and found a single major stenotic lesion in five They suggested the possibility of surgery in these patients which would seem reasonable on the basis of the poor prognosis in this syndrome[1] This step was taken by Silverman and Flamm[7] in a patient who showed a seg

mental obstruction of 75 per cent in his right main coronary artery We believe that with the development of selective coronary *arteriography and bypass sur* gery the exact diagnosis of a condition with the above mentioned pathological associations and a poor prognosis has special importance Since the history in this syn drome is atypical and both the resting and the exercise ECG are usually normal con tinuous ECG monitoring under dynamic conditions as described above is of par ticular assistance in diagnosing these cases

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Depression of cardiac performance by ethanol unmasked during autonomic blockade

*Maylene Wong, M.D.**
Los Angeles, Calif.

The published accounts of the hemodynamic effects of acutely administered ethyl alcohol on the cardiovascular system appear to be inconsistent.[1] The literature suggests that alcohol can both stimulate and depress the heart and in some instances produce no discernible change in hemodynamics. Plausible explanations for the variance are found in the differences among subjects and their preparation, in the dose of alcohol administered, and in the methods and timing of measurements. Conducting experiments in identical fashion in anesthetized dogs, we unexpectedly made all three observations of stimulation, depression, and apparent unresponsiveness. Consequently, it seemed to us that the observations might be valid and that another explanation for the inconsistency of the findings was wanting. Surmising that extracardiac stimuli, especially catecholamine release by alcohol, were obscuring alcohol's direct effect on cardiac performance, studies were combined with autonomic blockade. It is the purpose of this paper to present the data from these experiments and to offer a concept that makes the literature more consistent.

Methods

Twenty mongrel dogs weighing 20 to 31.7 kilograms were studied in the fasting state. All of the animals had been housed at our animal facility for at least three weeks before the experiment and had been fed with vitamin supplements once a day. Their general nutrition appeared to be good, and their hematocrits ranged from 39 to 55 per cent. Morphine sulfate 1.0 mg per kilogram of body weight was administered subcutaneously, and anesthesia was induced one hour later with chloralose 60 mg and urethane 600 mg per kilogram of body weight given intravenously. Thereafter, ⅕ to ¼ of the anesthetizing dose was added every 60 to 90 minutes. Ventilation with 100 per cent oxygen was assisted through a cuffed endotracheal tube and the volume and rate of the respirator were regulated to maintain arterial P_{CO_2} between 35 and 45 mm. Hg. Hyperinflation to 25 cm. H_2O was applied automatically every 5 minutes to minimize atelectasis. The electrocardiogram was monitored continuously, and body temperature was recorded periodically from a thermistor placed in the ascending aorta. Catheters

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were inserted through arterial and venous cutdowns into the left ventricle thoracic aorta pulmonary artery and inferior vena cava and were kept patent with periodic flushes of 4 per cent sodium citrate Aortic and left ventricular pressures were detected with Statham P23D strain gauges and zero reference for pressures was set at the midchest level Left ventricular end diastolic pressure was recorded at the highest amplifier gain and was read during end expiration The frequency response characteristics of the left ventricular catheter showed resonant frequencies between 30 to 40 cycles per second Cardiac output was estimated from duplicate indocyanine green dilution curves One ml of dye was flushed into either the pulmonary artery or left ventricle and blood was sampled at 38 2 ml per minute from the thoracic aorta *through* a Gilford densitometer The blood sample was reinfused after the inscription of each curve Calibration of the indicator was accomplished through the same catheter system using the animal s blood with the initial hematocrit and three dilutions of dye *Hematocrits* at the end of the experiments were always higher than those at the start by an average of four percentage points The difference between duplicate determinations of cardiac output was 5 5 per cent ± 1 2 (mean ± S E M)

Combined beta adrenergic and post ganglionic parasympathetic blockade was produced by an intravenous injection of 0 2 mg per kilogram of body weight of propranolol (dl propranolol) and 1 0 mg per kilogram of body weight of atropine and maintained by a constant infusion of propranolol 0 004 and of atropine 0 02 mg per kilogram of body weight per minute respectively [3] It has been shown in six anesthetized and atropinized dogs that after this initial dose of propranolol myocardial contractile force and heart rate do not respond significantly to stimulation of the left stellate ganglion (2 millisecond pulses at supramaximal voltage of 20 per second) or to intravenous injections of isoproterenol (0 4 mg per kilogram of body weight) for 20 minutes or more [3]

The animals were grouped into 8 dogs that received infusions of ethanol with autonomic blockade (E+B) 4 dogs that received infusions of saline with blockade (S+B) and 8 dogs that received ethanol without blockade (E−B) Six periods of observation were made in each experiment 2 control periods at 3 and 3½ hours after anesthesia which were also 30 and 60 minutes after autonomic blockade in the blockade experiments and 4 serial observations at 30 60 90 and 120 minutes after starting the infusions of ethanol or saline The infusion rates of alcohol ranged from 25 to 33 mg per kilogram of body weight per minute and averaged 29 mg per kilogram of body weight per minute for both ethanol groups and produced blood levels of ethanol over 100 mg per 100 milliliters by 30 minutes and over 200 mg per 100 milliliters by 2 hours [4] The concentration of ethanol was adjusted so that the volume was delivered at 2 ml per minute the same rate at which saline was infused

In 5 of the 8 dogs receiving ethanol with blockade and 2 of the 4 animals receiving saline with blockade 3 to 4 endocardial biopsies were sampled from the right ventricular endocardium during the experiment at spaced intervals for biochemical analyses that will be reported separately In our *hands this procedure* had no measurable effect on the hemodynamics judging from negligible changes measured in a group of 4 biopsied animals comprised of the 2 from the *present saline* with blockade group and 2 others that received glucose with blockade Mean *changes from* control measurements at the end of the 2 hour observation period were mean aortic pressure = −2 0 per cent *cardiac output* = +1 0 per cent *heart rate* = +4 0 per cent and left ventricular end diastolic pressure = +0 1 *mm Hg*

Results

Table I gives the mean values for *cardiac index* (CI) mean aortic pressure (MAP) *left* ventricular end-diastolic pressure (LVEDP) and heart rate for each group at control and experimental periods The only significant differences at the 5 per cent level of confidence between groups *during* the control period were a lower MAP *in* the ethanol with blockade (E+B) group and a slower heart rate in the ethanol *without blockade* (E−B) group The com

Depression of cardiac performance by ethanol unmasked during autonomic blockade

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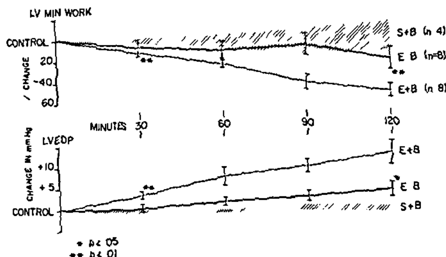


Fig 1 For each group *left ventricular minute work* (external work = cardiac index X mean aortic pressure) is expressed as the mean percentage change from control at each period Left ventricular end diastolic pressure is graphed as the mean change in mm Hg Limits represent one SEM Significance between the saline animals and each ethanol group was computed with Student's t test S+B = saline with blockade E−B = ethanol without blockade E+B = ethanol with blockade

vidual experiments during the first 30 minutes In Fig 1 the mean changes from control in left ventricular minute work and left ventricular end diastolic pressure are plotted for each group at each period of observation during the infusions This presentation of the data emphasizes the difference between the two ethanol groups Without blockade alcohol produced a downward trend in cardiac performance but none of the changes differed from the saline group until 120 minutes With blockade alcohol produced progressive impairment that was significant by 30 minutes and at all periods greater than in animals without blockade

Discussion

A comparison of recent canine studies on the hemodynamic consequences of acutely administered ethyl alcohol is complicated by differences in methods which of themselves can influence the over all results profoundly [4 5 12] The studies were conducted in dogs anesthetized with either pentobarbital or alpha-chloralose Barbiturates directly depress the heart[13] and both agents have opposite effects on heart rate which are mediated through changes in autonomic balance [14] All but two studies were carried out in the open-chest preparation which reduces heart volumes [15] While this effect is less relevant in preparations with controlled pressure and flow the thoracotomy itself produces a sympathetic preponderance in autonomic nervous activity [16] The administration of alcohol also varied from continuous infusions of 15 to 2 000 mg per kilogram of body weight per minute to bolus injections of 0 5 to 5 0 Gm per kilogram of body weight and the blood levels of alcohol achieved when available naturally also varied Hemodynamic measurements were recorded as early as 5 minutes after the beginning of the alcohol administration and in one series observations continued to 5 hours Results were expressed either in terms of the Frank-Starling relation of ventricular filling pressure to work or of contractility assessed from strain gauge analysis The differences in preparation and subsequent dissimilarities in results and interpretation that came from the same laboratory illustrate the importance of methods [10 12]

Despite the variation in methods among these studies a close examination reveals some uniformity of results when the average to concentrated dose schedules were used or where concentrations of blood alcohol rose to at least 1.0 mg per 100 ml In anesthetized dogs ethanol consistently

Table I Cardiac performance at control and during 2 hour infusions

	Control	During infusions (minutes)			
		30	60	90	120
Cardiac index (ml /min /kg)					
E − B	117 ± 14	111 ± 9	102 ± 9†	101 ± 11†	93 ± 11‡
E + B	115 ± 11	107 ± 11	92 ± 10§	76 ± 14§	67 ± 12§
S + B	127 ± 25	130 ± 26	126 ± 30	125 ± 29	126 ± 27
Mean aortic pressure (mm Hg)					
E − B	147 ± 6	139 ± 10	143 ± 9	142 ± 6	151 ± 6
E + B	132 ± 5	127 ± 6	128 ± 6	123 ± 8†	119 ± [illegible]‡
S + B	150 ± 10	145 ± 13	150 ± 11	148 ± 11	152 ± 9
Left ventricular end diastolic pressure (mm Hg)					
E − B	6 1 ± 0 9	6 5 ± 1 4	7 5 ± 1 3	9 3 ± 1 5	10 5 ± 1 [illegible]*
E + B	7 3 ± 1 3	10 8 ± 2 0	14 9 ± 3 1*	17 9 ± 2 5§	20 7 ± 3 8§
S + B	9 8 ± 2 1	9 5 ± 2 0	9 5 ± 2 2	10 3 ± 2 1	9 8 ± 2 5
Heart rate (beats/min)					
E − B	106 ± 10	105 ± 5	95 ± 5	97 ± 5	102 ± 6
E + B	139 ± 6	136 ± 7	139 ± 9	135 ± 7	134 ± 6
S + B	133 ± 10	132 ± 12	132 ± 11	135 ± 14	138 ± 14

Mean ± SEM E − B = ethanol without blockade E + B = ethanol with blockade S + B = saline with blockade
*p < 025
†p < 01
‡p < 005
§p < 001

parative reduction in the MAP is most likely fortuitous and is unrelated to the autonomic blockade as the control MAP in the saline with blockade (S+B) dogs was not reduced Morever, in 19 animals where the MAP was recorded before and after blockade, the means were essentially the same The control heart rates for the 2 blockaded groups are within one standard deviation of those reported in other blockaded dogs anesthetized or awake[2,5]

During ethanol infusions cardiac index declined and LVEDP rose in both groups but the changes were more pronounced in the blockaded dogs In the S+B group neigher CI nor LVEDP changed significantly throughout the period of observation Aortic pressure decreased from control only in the E+B group and the change was significant by the 90 minute period Heart rates remained unchanged from control in all 3 groups

To assess the effects of autonomic blockade measurements were taken before and after blockade in 19 animals which included all 12 dogs from the 2 blockaded groups Means before and one hour after continuous blockade for cardiac index were 114 and 106 ml per minute per kilogram of body weight (n s) for LVEDP 6 5 and 8 6 mm Hg (p = 0 05) for heart rate 108 and 137 (p < 0 005) and for MAP 130 and 132 mm Hg (n s) Temperatures in the ascending aorta showed no consistent change after blockade and during blockade, varying only 0 5 to 1 0° C in both directions

While the general trend for both groups of animals receiving ethanol was one of deterioration as judged from a rising LVEDP and a falling cardiac output the changes were more advanced in the E+B group and in the E−B group the changes were both upward and downward in indi

ments releases catecholamines mainly epinephrine from the adrenal medulla in man and dogs[28,30] it would then be available to stimulate the heart through the unblocked beta adrenergic receptors However the fact that the F−B group does ultimately show significant deterioration suggests that both stimulation of the heart by catecholamines and depression by ethanol were in force during the period of observation By comparison the E+B group devoid of extrinsic neurohumoral stimuli manifested only the direct depressant effect of ethanol on the heart Our results are similar to those of Nakano and co workers[8] who showed that in the open chest preparation the magnitude of myocardial depression from ethanol was markedly greater in dogs treated with reserpine than in untreated dogs

Thus our findings in the unblocked ethanol group differ but only quantitatively from the results of most of the studies carried out in anesthetized dogs Although alcohol eventually depressed cardiac performance hemodynamics within the first hour did not change significantly The apparent unresponsiveness to ethanol was due to individual experiments that showed variations in cardiac output and LVEDP in both directions Had we chosen a shorter duration of study our conclusions might have been different These quantitative differences between our results and those of others emphasize the importance of weighing the influence of an inotropic agent on the heart against other determinants of cardiac performance intrinsic myocardial function neurohumoral stimuli the presence of other cardiac stimulants and depressants and the interposition of the investigative methods themselves

The quantitative difference between our own two ethanol groups leads to the supposition that the negative inotropic response to alcohol can be obscured by extra cardiac stimuli in particular catecholamine release mediated through the autonomic nervous system This hypothesis can clarify much of the confusion arising from the hemodynamic results reported in human subjects In these investigations methods and quantities of alcohol used are surprisingly uniform (2 to 6 ounces of 84 to 90 proof) but the subjects are dissimilar in reference to heart disease

Four independent laboratories[31-34] studied the effects of a single drink of whiskey rum or gin taken by normal subjects at rest and found the cardiac output to be increased over control measurements Riff and colleagues[31] and Blomqvist and associates[32] further tested their youthful subjects with submaximal and maximal exercise respectively Both investigators showed that during effort heart rate and cardiac output rose to equivalent levels with and without alcohol

Catecholamine measurements following alcohol ingestion are sparse but they are uniform in showing an increase[28,30] In humans there is a 67 per cent increase in epinephrine excreted in urine[28] and in dogs at comparable doses of alcohol per unit of body weight blood epinephrine levels increase two to fivefold[30] Plasma norepinephrine rises only minimally with moderate doses of ethanol During exercise the increase in plasma catecholamines is from norepinephrine which rises from slightly above to several times over resting concentrations at submaximal to maximal levels of effort[3,35]

According to our supposition the release of epinephrine dominated any negative effect of alcohol in normal subjects at rest During exercise the generalized discharge of norepinephrine from nerve endings with its potent beta adrenergic stimulation of the heart totally masked any impairment from alcohol and for that matter obscured any weaker beta stimulation from epinephrine release

By comparison in alcoholics with no clinical evidence of heart disease 6 ounces of 86 proof alcohol produced no changes in heart rate cardiac output and blood pressure[37,38] Regan and associates[37] studied this group further and found that their response to angiotensin infusion was abnormal and when challenged with 12 ounces of alcohol showed a falling stroke output and rising LVEDP

In subjects with coronary heart disease and stable angina a small dose of alcohol resulted in a significant decline of cardiac output and systolic blood pressure both at rest and during light exercise[39] In another group of subjects with compensated clinical heart disease of different etiologies Gould

caused depression of cardiac performance with one possible exception In his most recent report Webb and colleagues[12] used a partial bypass preparation and held cardiac output heart rate and blood pressure constant Chloralose was the maintenance anesthetic and bilateral vagotomy was employed At blood levels of alcohol exceeding 600 mg per 100 ml per cent change in dp/dt did not vary and significant changes in LVEDP did not occur, although an illustration showed "more variation in the LVEDP than in most experiments" of approximately +10 mm Hg The conclusion was that ethanol did not have any appreciable effect on myocardial contractility and that the isolated heart lung preparation minimized peripheral effects of alcohol In the same preparation and at blood alcohol concentrations of 238 ± 16 mg per 100 ml Mierzwiak and colleagues[7] found similarly an insignificant decrease in maximum dp/dt associated with a statistically significant increase in LVEDP of only +2 5 cm H_2O however they concluded that the heart was depressed

Our methods resembled most closely those of Regan and associates[4] who used closed chest, anesthetized (pentobarbital) dogs and a continuous infusion of alcohol at a dose less concentrated than ours By 15 minutes the left ventricle was ejecting a reduced stroke output at a higher LVEDP In our comparable ethanol without blockade group (E−B) half of the dogs showed increases in cardiac output and another half showed decreases in LVEDP by 30 minutes Not until the second hour did the hemodynamics demonstrate significant changes in both cardiac output and LVEDP These quantitative differences can best be explained by the difference in anesthetic agents used and were observed by Mierzwiak and colleagues[7] who employed chloralose in some dogs and pentobarbital in others

The earlier and more severe depression of cardiac performance seen in the group with alcohol and blockade must be interpreted in relation to any influence the blocking drugs may have had on the heart Although large doses of propranolol directly depress myocardial function [17,18] smaller beta adrenergic blocking doses have no depressant effect in hearts already deprived of adrenergic activity [3,14,19,20] as is the case in our blockaded groups Atropine, given alone in doses 10 to 5 times smaller than ours, does not depress ventricular function curves in right heart bypass preparations,[1] nor does it change blood pressure, heart rate, or coronary blood flow in denervated hearts [22] The direct effect of larger doses of atropine on the myocardium of dogs is unknown Combined autonomic blockade with both agents in our own series of anesthetized dogs did not alter cardiac output although the heart rate was accelerated The mean change in LVEDP was +2 0 mm Hg and was just significant at the 5 per cent level Autonomic blockade in the unanesthetized dog with propranolol and vagal cooling changed the heart rate upward and stroke volume downward but not their product it did not change LVEDP [5] Similar results in normal human subjects attest to the lack of depressant effects of pharmacologic isolation of the heart [3,23]

If autonomic blockade does not reduce cardiac function to what is the difference between our two ethanol groups due? Since the directional change for both groups of animals is downward (Fig 1) the difference between the two represents for the E−B group less depression of cardiac performance in the presence of intact adrenergic and cholinergic functions While the precise balance between these two functions is unknown at any given moment the consistent acceleration of heart rate following autonomic blockade in our animals as well as in others[2,5] suggests that the prevailing nervous activity before blockade in chloralosed dogs and in conscious dogs[5] is that of vagal preponderance Accumulating evidence has corroborated that efferent vagal activity inhibits heart rate and function[24-26] and conversely that blockade of vagal activity increases ventricular rate and output [27] Thus the presence of intact parasympathetic function in the E−B group does not offer an explanation for its more favorable performance over the E+B group On the other hand intact adrenergic function could explain the difference between the two ethanol groups Since it is known that alcohol in doses both smaller and larger than those used in our experi

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and co-workers[34] found that only 2 ounces of whiskey diminished cardiac index at rest.

The hemodynamic studies in human subjects can thus be arranged into a continuous spectrum of responses that range from stimulation to depression. The character of the response seems most closely related to the functional capacity of the heart balanced against the presence of both the stimulatory effects of catecholamine release and the depressant effects of ethanol. It is not surprising that different laboratories using low to moderate doses of alcohol have observed (1) an augmentation of cardiac performance in normal subjects, (2) an apparent unresponsiveness in subjects with subclinical heart disease, and (3) a decline of cardiac function in patients with clinical heart disease.

Summary

Experiments from this and other laboratories have indicated that ethanol can both stimulate and depress cardiac function. Surmising that extracardiac stimuli, especially catecholamine release by alcohol, were obscuring its direct effect on the heart, studies were combined with autonomic blockade in anesthetized closed chest dogs. Ethanol was infused at rates of 25 to 33 mg. per kilogram of body weight per minute; autonomic blockade was achieved with an initial dose of atropine 1.0 mg. per kilogram of body weight and propranolol 0.2 mg. per kilogram of body weight and maintained by constant infusion. Cardiac performance was assessed from the Frank-Starling relation of ventricular filling pressure to cardiac work at control and at intervals after the start of infusions. Saline infusion with blockade caused no change in cardiac performance over 120 minutes. Ethanol with blockade caused progressive falls from 30 minutes on. Alcohol without blockade produced rises and falls in different animals in the first 30 minutes; thereafter cardiac performance declined but at all intervals less than in dogs given alcohol with blockade.

We concluded that alcohol uniformly depressed the heart after autonomic blockade but without blockade this effect could be masked by extracardiac mechanisms mediated through the autonomic system. Assuming that catecholamine release was an important extracardiac mechanism, the conclusion was tested against conflicting reports in the literature and was found to be a useful hypothesis.

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Investigation of atrial aberration as a cause of altered P wave contour

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Explaining a changing P wave contour is oftentimes the bane of the electro cardiographer Sudden variation in P wave morphology is generally due to a change in the site of atrial focus such as occurs in *atrial premature contractions* or *atrial escape beats* Gradual variations in P wave contour are alternatively explained on the basis of a *wandering pacemaker* whereby it is assumed that the focus of atrial excitation moves gradually from one portion of the atrium to another *Atrial fusion* is characterized by depolarization of the atria via two origins simultaneously usually the sinus and an ectopic focus and this is yet another mechanism of changing P wave morphology One additional mechanism proposed to explain sudden changes in P wave contour—and that which is the subject of this study—is aberrant impulse conduction through the atria (*atrial aberration*)[1,2] Here, it is proposed that the site of impulse formation remains fixed but because portions of the atria are partially or totally refractory when the wave front reaches them, the impulse is forced to take an alternate course resulting in morphological changes in the P wave contour This particular mechanism may be considered analogous to aberrant ventricular conduction whereby gross changes in the QRS appearance come about when refractory fascicular, Purkinje or ventricular tissue is encountered by the depolarizing wave front[3-5] By infringing on the refractory period of the previous beat then premature supraventricular contractions or runs of supraventricular tachycardia could be aberrantly conducted through the atrium or ventricle resulting in variation of P wave morphology or in a distorted QRS complex Aberration of an escape beat—one which follows a pause—has also been described[5]

It should be pointed out that morphological changes in P wave contour also occur consequent to pathological changes within the atrium or atrial enlargement but such distorted P waves tend to be "persistent"—present in all the beats—rather than being intermittent

Although ventricular aberration is an unequivocal cause of striking changes in QRS duration and morphology variations

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in P wave contour resulting from this mechanism are more speculative and the phenomenon of atrial aberration is yet to be investigated systematically This study then was undertaken in order to test whether aberrant conduction within the atrium is in fact capable of altering P wave morphology and if such is the case whether the changes in P wave contour are marked—producing a total reversal of polarity—or only slight resulting in minor variations in P wave duration or appearance It is presumed that information derived from this study will enhance an understanding of atrial electrophysiology and should aid the clinician in comprehending complex electrocardiographic tracings

Method

Twenty three healthy adult mongrel dogs weighing 15 to 23 kilograms were anesthetized with sodium pentobarbitol (30 mg per kilogram of body weight intravenously) Respiration was maintained through a cuffed endotracheal tube attached to an automatic volume respirator pump One femoral vein was cannulated for the injection of drugs a pressure catheter was inserted into the right atrium via the other femoral vein and a femoral artery was cannulated for monitoring blood gases and pH Right or bilateral thoracotomies in the fourth intercostal space were performed and the heart was suspended in a pericardial sling Electrodes composed of gold tipped stainless steel needles fixed in plastic 2 mm apart were sutured with 4 0 cardiovascular silk to five sites on the epicardial surface of the right atrium (1) the region of the sino atrial node (2) the junction of the coronary sinus with the right atrium (3) the junction of the superior vena cava with the right atrium (4) the junction of the inferior vena cava with the right atrium and (5) the anterior mid portion of the AV groove These multiple electrodes were employed to observe lateral longitudinal and anteroposterior direction of the 1 vector in order to enhance the possibilities of detecting any change in P wave morphology The electrodes at the sinoatrial and coronary sinus sites acted as bipolar pacing electrodes and those from the vena cavae and AV groove served as unipolar recording electrodes In three dogs additional electrodes were secured on the left atrial surface at three sites pacing and recording electrodes at the center of the free wall of the left atrium and another recording electrode at the left atrial portion of Bachmann s bundle Standard limb Leads I II and III were also monitored

S_4 and S_8 Grass pulse generators connected through Grass isolation units and constant current units delivered both the driving and premature pulses through the same electrode A switch that simultaneously turned off the driving stimulus (S_0) triggered the atrial premature stimuli either singly (S_1) or in pairs (S_1 and S_2) The S_1 impulse was positioned at the S_0 effective refractory period (ERP) by moving the S_1 stimulus in at 5 msec intervals until it no longer produced a propagated response S_2 was positioned at the S_1 ERP in the same manner The stimulus strength for S_0 S_1 and S_2 was set at 2 Ma above threshold threshold was defined as the minimum amperage necessary to drive the heart at a given rate Only *paced* premature and postextrasystolic beats were evaluated for aberration to eliminate atrial ectopy as causes of P contour change Atrial fusion was also avoided by having the paced beats precede unpaced ones

Because the premature P often hit upon the T wave of the preceding beat change in its configuration was difficult to evaluate For this reason complete heart block was produced in 10 dogs by making an incision through the AV node The production of complete heart block allowed the delivery of P waves late in ventricular diastole after completion of the T wave A purse string suture of 3 0 silk was secured around the right atrial appendage and the tip of the appendage was removed to provide entrance into the right atrium A small knife designed to fit flat against the index finger was inserted the site of the AV node located by palpation and a cut approximately 1 cm long was made through the AV node More than one cut was made if the first failed to produce complete heart block The hearts were examined after the study was terminated and in seven hearts the cut through the AV node extended to the atrial septum Comparing these studies with the three in which the

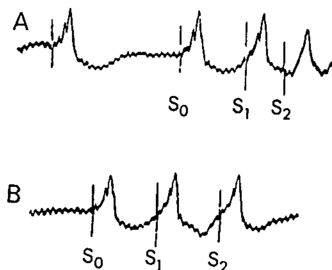


Fig 1 A and B Electrically stimulated P waves are recorded from Lead II A the P wave of the first premature stimulus (S_1) does not differ significantly in configuration from the normally paced beats (S_0) The P wave following the second premature stimulus (S_2) is slightly smaller and less notched B Lesser degrees of prematurity result in the abolition of atrial aberration Complete heart block is present in both tracings and QRS complexes are not seen

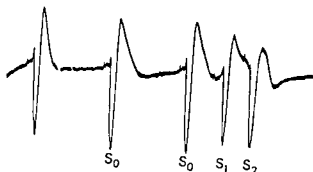


Fig 2 Atrial electrograms taken when the region of the sinoatrial node is stimulated the recording is being taken from the region of Bachmann s bundle The P waves following both the first and second premature stimuli (S_1 S_2) differ slightly in contour from the normally paced beats (S_0) and also differ slightly from each other Complete heart block is present and QRS complexes are not evident Note the atrial repolarization waves

septum was not damaged yielded no significant differences in the frequency of or degree of aberration, so the 10 studies are considered together After AV block was obtained a pulse of 2 msec duration drove the atria at a rate of three to four cycles per second the rate and duration were held constant throughout the experiment The right ventricle was intermittently paced at a rate of 1 5 to 2 5 cycles per second to maintain the heart's viability

In four dogs, additional studies in the normally conducting heart were undertaken to clarify the role of right atrial pressure (or myocardial stretch) on P wave contour Two methods were used to increase atrial pressure (1) rapidly injecting four consecutive 100 ml boluses of Ringer s lactate solution into the right atrium through the femoral venous catheter raising the pressure from between 6 and 14 mm Hg, and (2) inserting a balloon through the wall of the right ventricle and gradually inflating it Paced and unpaced recordings were taken during the injection and balloon inflation to evaluate the effect of these maneuvers on P wave configuration when the cycle length was held constant

All recordings were made on a Honeywell multichannel photographic recorder Two channels recording atrial and one standard limb lead were recorded simultaneously

Changes in P wave morphology were described in terms of amplitude contour and duration The effects of five variables on atrial aberration were considered (1) the degree of prematurity of the premature beats evaluated in all studies by comparing the premature beats (S_1 and S_2) to each other and to the paced beat (S_0) (2) stimulus strength considered in five studies by comparing S_1 and S at the standard stimulus and at four to tenfold multiples of the standard strength (3) influence of differing stimulus sites (4) influence of changing heart rate (atrial pacing rate) and (5) effect of increasing atrial pressure or stretch on P wave configuration

Results

Complete heart block preparations The P wave contour could be studied most precisely—without becoming superimposed on the preceding T wave—under conditions of complete heart block In these studies only minor changes in P wave amplitude duration and contour appeared as the prematurity became greater and the premature P wave was made to impinge upon the effective refractory period (ERP) of the preceding beat In limb Leads I II and III we observed amplitude changes ranging from $-0\ 093$ to $+0\ 15$ mv ($\pm 9\ 9$ per cent) duration changes ranged from $-0\ 10$ to $+12$ msec (± 6 per cent) and slight

contour changes such as minor degrees of notching were elicited in the premature impulse (S_1) (Figs 1 and 2) As the S_0 S_1 coupling interval was gradually widened the changes in amplitude duration and contour progressively became less marked until the premature beat appeared to be identical with the paced beat (Fig 1) It should be emphasized that the changes in P wave contour noted were slight often absent and there were no instances where P wave polarity became reversed—i e when a negative P wave became positive or vice versa

Introducing pairs of premature stimuli (S_1 S) also elicited minor changes in amplitude (−0 26 to +0 22 mv ±14 per cent change) duration (−20 to +10 msec) and minor degrees of notching seen in the limb leads Although the configurations of the first and second premature P waves often differed slightly from one another the over all changes continued to be slight and still no marked variation in P wave contour or reversal in polarity was detected (Figs 1 and 2) When the atrial pacing rate was suddenly increased the initial P waves showed minor changes similar to those described above however the subsequent beats reverted to the original P wave morphology

Increasing the strength of the premature impulse by 4 to 10 times stimulus threshold permitted a greater degree of prematurity since further penetration into the S_0 effective refractory period could be accomplished and this resulted in amplitude duration and contour changes slightly exceeding those described above However variations in the appearance of the P wave remained notably slight Increasing the strength of the premature stimulus without changing coupling interval did not affect P wave morphology

It was thought possible that certain pathways within the atrium might be more vulnerable to the development of atrial aberration than others This hypothesis was looked into by stimulating the atrium from three different electrodes No particular pattern was evident in these studies—i e the frequency and minor degrees of aberration seen were the same whichever stimulus sites were employed

Finally it was noted that slight changes

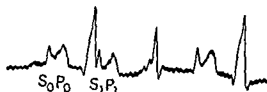


Fig 3 Lead II recorded in a preparation which has no complete heart block The premature P wave (P) is shown to manifest slight aberration being smaller and slightly more peaked The larger complexes are QRS s



Fig 4 The P wave contour is seen before (A) and after (*B*) inflating a balloon in the right ventricle Note that the P wave becomes slightly more peaked and the notch moves onto its upstroke

in the pacing (S_0) P wave configuration occurred with the production of complete heart block In 7 of the 10 studies the induction of complete block resulted in slight injury to the atrial septum The results from these studies were indistinguishable from those where the septum remained intact leaving us to conclude that septal injury per se did not influence the degree of aberration observed

Absence of complete heart block In the studies in the normally conducting heart we evaluated both the premature and postextrasystolic beat for aberration Again both types of beats showed only slight—at times negligible—changes in amplitude contour and duration (Fig 3) Oftentimes the beats fell upon the T wave of the preceding beat making it difficult to determine whether prematurity or superimposition on the T wave was more responsible for the contour change In those studies in which the T wave was small or isoelectric the P change could be quantitated decreases in P wave duration up to 5 msec and/or amplitude up to 0 10 mv

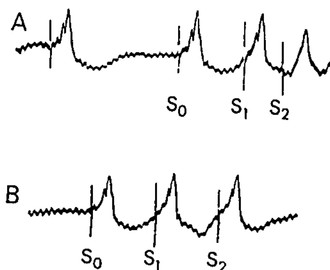


Fig *1* *A* and *B* Electrically stimulated P waves are recorded from Lead II [illegible] the P wave of the first premature stimulus (S_1) does not differ significantly in configuration from the normally paced beats (S_0) The P wave following the second premature stimulus (S_2) is slightly smaller and less notched *B* Lesser degrees of prematurity result in the abolition of atrial aberration Complete heart block is present in both tracings and QRS complexes are not seen

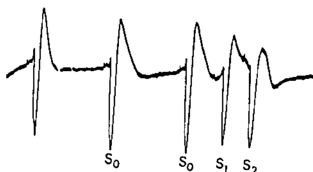


Fig *2* Atrial electrograms taken when the region of the sinoatrial node is stimulated the recording is being taken from the region of Bachmann s bundle The P waves following both the first and second premature stimuli (S_1 S_2) differ slightly in contour from the normally paced beats (S_0) and also differ slightly from each other Complete heart block is present and QRS complexes are not evident Note the atrial repolarization waves

septum was not damaged yielded no significant differences in the frequency of or degree of aberration, so the 10 studies are considered together After AV block was obtained, a pulse of 2 msec duration drove the atria at a rate of three to four cycles per second the rate and duration were held constant throughout the experiment The right ventricle was intermittently paced at a rate of 1 5 to 2 5 cycles per second to maintain the heart s viability

In four dogs additional studies in the normally conducting heart were undertaken to clarify the role of right atrial pressure (or myocardial stretch) on P wave contour Two methods were used to increase atrial pressure (1) rapidly injecting four consecutive 100 ml boluses of Ringer s lactate solution into the right atrium through the femoral venous catheter raising the pressure from between 6 and 14 mm Hg, and (2) inserting a balloon through the wall of the right ventricle and gradually inflating it Paced and unpaced recordings were taken during the injection and balloon inflation to evaluate the effect of these maneuvers on P wave configuration when the cycle length was held constant

All recordings were made on a Honeywell multichannel photographic recorder Two channels recording atrial and one standard limb lead were recorded simultaneously

Changes in P wave morphology were described in terms of amplitude contour, and duration The effects of five variables on atrial aberration were considered (1) the degree of prematurity of the premature beats, evaluated in all studies by comparing the premature beats (S_1 and S[illegible]) to each other and to the paced beat (S_0), (2) stimulus strength considered in five studies by comparing S_1 and S_2 at the standard stimulus and at four to tenfold multiples of the standard strength (3) influence of differing stimulus sites (4) influence of changing heart rate (atrial pacing rate) and (5) effect of increasing atrial pressure or stretch on P wave configuration

Results

Complete heart block preparations The P wave contour could be studied most precisely—without becoming superimposed on the preceding T wave—under conditions of complete heart block In these studies only minor changes in P wave amplitude duration and contour appeared as the prematurity became greater and the premature P wave was made to impinge upon the effective refractory period (ERP) of the preceding beat In limb Leads I II and III we observed amplitude changes ranging from −0 093 to +0 15 mv (±9 9 per cent) duration changes ranged from −0 10 to +12 msec (±6 per cent) and slight

troversy as to whether impulse propagation through the atrium depends upon the specialized interatrial tracts or whether atrial depolarization simply progresses in a quasi radial fashion corresponding to the gross anatomical landmarks[8,9] We reasoned that assuming these tracts are physiologically significant they would in all likelihood have nonidentical refractory periods Thus a sufficiently premature stimulus might encounter a pathway which was incapable of normal conduction and the morphology of the P wave would thereby be grossly altered This is precisely what is seen in ventricular aberration where gradual increments in prematurity often lead to the sudden appearance of right bundle branch block * We therefore compared the effects of different sites of stimulation on the degree of atrial aberration speculating that an impulse originating from a particular locus might manifest a more marked degree of aberration were it to normally utilize an atrial pathway and were it to encounter refractoriness of that particular tract[10] The results of this portion of the study were clear only *gradual* or *slight changes* in P wave morphology were detected in our study as the degree of prematurity was increased and the magnitude of change was uninfluenced by location of the stimulating impulse These findings therefore indirectly suggest that the internodal tracts play only a minor role in impulse spread through the atria An alternative explanation of these data would be that the refractory period of all the tracts and of the atrial musculature are essentially uniform Thus the evidence that these tracts are physiologically important (P wave alterations are seen in experimental animals after *focal* lesions have been produced at sites of interatrial tracts[11]) cannot be negated by these findings

The second observation of note was that increased atrial fiber stretch or pressure—in the presence of a fixed heart rate—produced essentially the same morphological P wave alterations as did varying cycle length A premature atrial contraction often occurs when the AV valves are closed or when the ventricular relaxation is incomplete suggesting that this mechanical effect on P wave contour might be as important as the temporal effect Transient alterations in P wave configuration also occur in certain clinical situations such as acute cor pulmonale status asthmaticus and in left ventricular failure following acute myocardial infarction—conditions where an atrium is temporarily dilated The mechanism by which atrial stretch or pressure influences the appearance of the P wave is unknown and might include slight rotations of the heart or the effect of atrial stretch on cellular membrane potential or atrial conduction Whatever the underlying mechanism one is forced to conclude that the aberrant atrial beats detected in this study might be related either to their timing or to varying fiber tension or stretch

The final point of emphasis is that the changes we observed in P wave morphology were slight much less in degree than most of the P wave alterations we usually try to explain in clinical electrocardiography Thus were we to extrapolate from animal studies to clinical situations—a step that should be taken with some caution—we would conclude that most of the gross changes in P wave contour are related to factors other than aberrancy wandering atrial pacemaker atrial or junctional ectopy fusion beats respiratory effects or artifact Clinical electrocardiography remains sufficiently speculative so that it would seem unwise at this time to invoke a mechanism such as atrial aberration to explain all but the most minor alterations in P wave configurations seen

Summary

In order to study atrial aberration atrial premature beats and postextrasystolic beats were electrically induced in 23 dogs and the P wave contour was recorded in limb and atrial leads In these studies the site and timing of stimulation were controlled to eliminate ectopy and fusion as causes of P wave change Further P wave analysis was facilitated by producing complete AV block in 10 dogs thereby

appeared in the premature or postextrasystolic beat

Right atrial volume and pressure change When right atrial volume was *suddenly* or gradually increased by volume expansion or by inflating a balloon in the right ventricle alterations in P wave duration amplitude, and contour similar to those seen during premature stimuli were noted, even though cycle length was held constant (Fig 4) Duration varied by ±10 msec, amplitude changed by ±14 mv, and again only slight degree of P wave notching without reversal of polarity was detected The greatest changes in P wave morphology were produced with the greater degrees of pressure and volume

Discussion

This study was designed to determine whether aberrant conduction through the atrium might be one mechanism of producing transient alterations in P wave morphology Before delving into the subject further it is important to establish certain definitions Aberrancy is the term generally applied to describe temporary alterations in P or QRS configuration brought about when an impulse reaches tissue which is refractory and therefore incapable of allowing normal conduction Excluded from the definition of aberrancy then are alterations in P or QRS configuration due to ectopic foci to fusion or to more permanent conduction disturbances consequent to myocardial degeneration infiltration or fibrosis

Ventricular aberration is a well accepted entity and occurs when a supraventricular impulse encounters an incompletely repolarized bundle branch or fascicle[3,5] This most commonly is seen in a premature beat or during tachycardia where the shortened cycle length enhances the likelihood that the impulse will infringe upon the refractory period of the preceding beat Cardiac slowing also increases the possibility that a subsequent premature beat (with a shortened cycle length) will encounter refractory fibers, so that the combination of a long interval followed by a short interval constitutes the most favorable set of circumstances for the production of ventricular aberration[3,5] Since the refractory period of the right bundle branch exceeds that of the AV node, His bundle and left bundle branch, functional right bundle branch block is the most common form of ventricular aberration seen *Paradoxical aberration*, the appearance of a distorted QRS complex which appears following a *pause* is observed less commonly but remains a well established entity[5]

The concept of *aberrant atrial conduction* has been invoked to explain bizarre configurations of the sinus P wave following premature atrial AV junctional and ventricular contractions[1,2] Chung and colleagues studies[1,2] consisted of reviewing clinical electrocardiograms and the P waves considered to show atrial aberration were those terminating the postextrasystolic pause We presume that these P waves, rather than the premature ones were studied since in clinical electrocardiography one is unable to exclude atrial ectopy as a cause of P wave alteration in premature beats Thus although atrial aberration is more likely to occur during a shortened cycle length Chung and colleagues[1,2] were obliged to concentrate only on the P waves ending a prolonged cycle in their search for atrial aberration One should point out at this juncture that even under these circumstances ectopy or fusion of the escaped beat cannot be excluded as a potential cause of altered postextrasystolic P wave configuration

The conditions were set in our present study to optimize the chances of detecting changes in P wave configuration due to aberrant conduction At the same time controlling factors were built in to eliminate atrial ectopy wandering pacemaker and atrial fusion as potential complicating factors which might influence P wave contour Under these controlled conditions only minor changes in P wave morphology and duration were observed marked abnormalities such as reversal of P wave polarity were never seen Thus although cycle length was varied and excessive prematurity produced (to the point of reaching complete atrial refractoriness) and beats following postextrasystolic pauses were studied only minimal degrees of aberrant atrial conduction were seen

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troversy as to whether impulse propagation through the atrium depends upon the specialized interatrial tracts or whether atrial depolarization simply progresses in a quasi radial fashion corresponding to the gross anatomical landmarks[6 9] We reasoned that assuming these tracts are physiologically significant they would in all likelihood have nonidentical refractory periods Thus a sufficiently premature stimulus might encounter a pathway which was incapable of normal conduction and the morphology of the P wave would thereby be grossly altered This is precisely what is seen in ventricular aberration where gradual increments in prematurity often lead to the sudden appearance of right bundle branch block * We therefore compared the effects of different sites of stimulation on the degree of atrial aberration speculating that an impulse originating from a particular locus might manifest a more marked degree of aberration were it to normally utilize an atrial pathway and were it to encounter refractoriness of that particular tract[10] The results of this portion of the study were clear only *gradual* or *slight changes* in P wave morphology were detected in our study as the degree of prematurity was increased and the magnitude of change was uninfluenced by location of the stimulating impulse These findings therefore indirectly suggest that the internodal tracts play only a minor role in impulse spread through the atria An alternative explanation of these data would be that the refractory period of all the tracts and of the atrial musculature are essentially uniform Thus the evidence that these tracts are physiologically important (P wave alterations are seen in experimental animals after *focal* lesions have been produced at sites of interatrial tracts[11]) cannot be negated by these findings

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* Admittedly ble d m m d g ee f be t oft bse d tl QRS comple with g t r ty ((mile ncomple ght b dle branch block) t t he ic l could g t al rea t d the dd ipe nc of mil t ight l ft b dl b h block lt t k g l g QRS morphology

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Case reports

Viral infection of the aorta of man associated with early atherosclerotic changes

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J M Harb Ph D
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The production of experimental atherosclerosis has been accomplished in numerous primates and other species by inducing hypertension and by dietary production of hyperlipemia[1] Furthermore attempts have been made to study the regression of aortic fatty lesions following cessation of high cholesterol diets[2-4] The most prominent feature of such atherosclerotic aortic lesions whether progressive or regressive has been the presence of lipid-containing cells in the aortic intima and in the inner elastic layers of the media The lipid-containing cells were considered by some investigators to be monocytes which had infiltrated into the aortic intima[4] whereas others have considered that foam cells are the predominant lipid containing cells in experimentally induced atherosclerotic lesions[5] In proliferative (non necrotic) lesions in monkeys the predominant cells observed were smooth muscle cells with fewer cells resembling fibroblasts[6]

The purpose of this report is to describe the finding of lipid-containing cells in the intima muscularis and internal elastic layer of the media of the aorta of a patient who had viral cardiomyopathy most probably due to the Coxsackie B_4 virus Lipid deposition suggestive of atherosclerotic alteration was found in the aorta of this patient It is suggested that the lipid deposition occurred as a response to a viral infection of the aorta itself an initiating stimulus other than hypertension or high cholesterol diet.

Case report

This 19 year old man was in excellent health until two weeks prior to his admission to hospital in Monroe Louisiana, on February 23 1972 for congestive heart failure He had gradually developed swelling of the abdomen and feet with mild dyspnea following an episode of diarrhea nausea and vomiting after eating pork on February 9 1972 Other than a past history of familial asthma treated with Primatene most of his life there was no apparently significant illness However he had had the usual respiratory diseases Examination on admission to hospital revealed generalized cardiomegaly loud first and second mitral valve sounds protodiastolic gallop rhythm and a soft systolic blowing murmur along the lower left sternal border There was a trace of edema of the ankles with elevated venous pressure

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preventing superimposition of the premature P on the preceding T wave

As the coupling interval was progressively narrowed minor changes in the premature P duration amplitude, and contour (such as slight degrees of notching) appeared The postextrasystolic P wave manifested even lesser changes Varying the myocardial stretch by changing right atrial volume produced similar alterations in P wave configuration at a constant cycle length Comparable variations in atrial stretch occur with premature beats and these mechanical effects may, therefore, be one mechanism of the P contour change

Atrial aberration was uninfluenced by site or strength of stimulus and was minimally affected by rate No reversal in P wave polarity was observed

We conclude that only small alterations in P configuration result from atrial aberration and that this mechanism should not be invoked to explain any but the most minor alterations in P wave configuration

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in New Orlean multiple views of the chest with barium in the e ophagus revealed marked general ized cardiomegaly (Fig 1) The electrocardio ram showed low voltage of all complexe and atrial flutter with 2 1 block (Fig 1) The ventricular rate was 125 beats per minute with an occasional ventricular premature contraction Digoxin was administered in oral doses to a total of 1 5 mg during the initial 4 days of hospitalization Quinidine sulphate 200 mg orally every 6 hour wa started on the second ho pital day On the fourth hospital day the patient s heart rate was 70 beats per minute Except for a short period when he had atrial fbrillation which converted to a normal sinus rhythm with a PR interval of 0 2? sec the patient seemed markedly improved However later the same day as he turned to the left lateral decubitus position for better auscultation of the mitral diastolic rumble he devel oped ventricular tachycardia and convulsed He was electrically cardio erted and was tran ferred to the medical inten ive care unit (MICU) Digitalis and quinidine were discontinued A xylocaine drip of 0 5 mg per minute controlled multifocal ventricu lar premature contractions Atrial flutter with 2 1 block recurred

Chest x ray the following day showed a large left pleural effusion which yielded 1 000 c c of transudative fluid on thoracente i A chest x ray after thoracente is revealed an inf ltrate in the left lower lobe and the pat ent was started on ampicillin intravenou ly

He remained in the MICU with sodium restric tion bed rest antibiotic and a quiet atmo phere He did well unt l the fourteenth ho pital day when he developed a temperature of 104 F and rigor The left pleural effu ion had reaccumulated Kantrex was added to the regimen and 500 c c of transudate we e removed by left thoracente

The patient continued to ha e fever Hi urine output dimini hed his ascite increased and his neck veins became more engorged The sputum culture revealed Kleb ella organi ms sensitive to Garamycin Becau e of a ri ng blood urea nitrogen and creatinine Kantrex and Ampicillin were discon tinued and he was given a mall dose of Garamycin Intermittent admin tration of La ix intravenou ly p oduced only light d re i Digitali wa withheld beca i e of continued ventricular premature con traction

On the twent eth hosp tal day he wa confused and letharg c Lumbar puncture wa no mal except for an opening pre ure of 290 mm H_2O due to the high ystem c enou pre ure The dosage of La ix was increased to 120 mg intra e ou ly and pro duced diure Garamycin was admin te ed e ery other day and the pat e it became afebrile A third left thoracente i removed 1200 c c of tran u date

O i the th ty second day the dig tali med cation wa va ied u g Ced lanid and later t ncture of d gital The patient developed hort period of vent cular tachyc ard a which re ponded to 100 mg of xyloca ie intravenou ly On the forty second hospital day he developed ventric ilar f b illat on and w defb ill ted The ascites increased and atri l flutter per i ted He finally became un re pon ive to the digitali a d variou diuretic

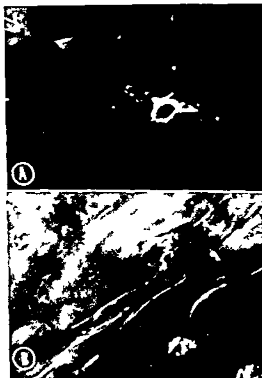


Fig 2 A and B Immunofluorescent Coxsackie B₄ ant body staining of the aorta of the patient with Coxsackie B viral infection Panels A and B show stained cytoplasm of cells in the adventitia (Hema toxylin and eo in Orig nal magn fication X125)

He died on May 17 1972 7? days after admis ion to Charity Ho pital in New Orleans

Methods and materials

Aortic tissue was obtained at autopsy 4 hours after death The tissue was then stored on ice for 8 hours before fixation in order to assure minimal postmortem changes although it had previously been shown that the cellular differences between 3 and 24 hours postmortem were not sig nificant in the aorta [7] Grossly the aortic wall had very small scattered whitish spots on the intimal surface otherwise it was of normal appearance The tissues were cut to provide longitudinal and cross sectional orientation and were processed for study by immunofluorescent staining light microscopic and electron microscopic techniques

Immunofluorescent staining method Fresh frozen tissues were cut in sections about 10 μ thick and were fixed in acetone for 10 minutes After rinsing with phosphate

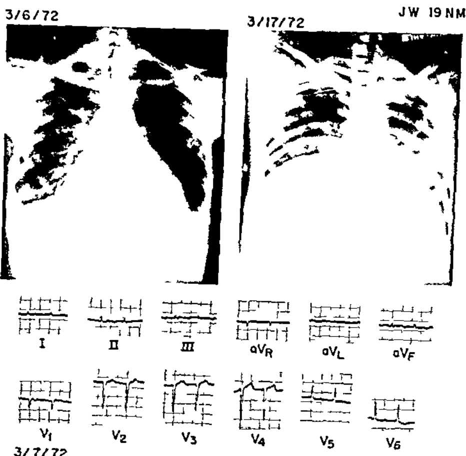


Fig. 1 Teleoroentgenograms of the heart and electrocardiogram of the patient with Coxsackie B_4 viral cardiomyopathy at time of admission to Charity Hospital in New Orleans

but no detectable hepatomegaly The *electrocardiogram* showed atrial flutter with 2 1 A V block

After 10 days of hospitalization and treatment with 20 units of digitalis leaf there was no improvement The patient began to have frequent premature ventricular contractions and on March 6 1972 was transferred to Charity Hospital in New Orleans

Physical examination on admission to Charity Hospital revealed a very thin and weak Negro man with an arterial blood pressure of 110/90 mm Hg without paradoxical variations The heart and pulse rates were 136 beats per minute and regular respiratory rate was 20 per minute and temperature 98 6 F There was a mild acneform rash over face and upper back The neck veins were markedly distended and there were large *a* waves Few scattered expiratory wheezes and basilar crepitant rales with decreased fremitus increased dullness and decreased breath sounds were noted at the bases of both lungs A right ventricular heave loud mitral first sound and loud protodiastolic gallop rhythm at the apex were present A Grade II/VI blowing systolic murmur and a faint diastolic rumble localized to the lower left sternal border in the fourth intercostal space were also present The murmur did not change with respiration The abdomen was slightly protuberant and nontender with a fluid wave and shifting dullness present The liver was not enlarged There was 3+ pitting edema of the feet and legs up to the knees and 3+ post sacral edema The patient was *slightly lethargic* with poor attention span

The *laboratory* findings on admission were *hemoglobin* 13 1 Gm per cent hematocrit 40 7 per cent white blood count 8 400 with normal differential erythrocyte sedimentation rate 4 mm per hour disulfide preparation negative lupus erythematosus preparation negative antistreptolysin O titer 1/50 Todd units creatine phosphate negative Latex RA negative fasting blood sugar 78 mg per cent blood urea nitrogen 14 mg per cent creatinine 0 7 mg per cent uric acid 3 6 mg per cent sodium 131 mEq per liter potassium 4 8 mEq per liter chlorine 101 mEq per liter CO 29 vol per cent calcium 9 3 mg per cent phosphorus 4 5 mg per cent bilirubin 1 6 serum glutamic oxaloacetic transaminase 130 creatine phosphokinase activity 295 lactic dehydrogenase 560 total serum proteins with A/G ratio 6 7 (3 7/3 0) urinalysis normal with specific gravity of 1 020 and pH of 6 0 Blood was type O and Australian antigen mono screening and febrile agglutinins for Typhoid A Typhoid O Paratyphoid B Proteus OX 19 and Brucella were all negative

Hospital course On admission to Charity Hospital



Fig 4 Photomicrograph of the media of the aorta of the 19 year old patient with Coxsackie B_4 viral infection Interstitial edema is associated with displacement of the elastic lamellae and smooth muscle cell (Hematoxylin and eosin Original magnification ×200)

hour each The tissues were embedded in flat molds with appropriate orientation Polymerization proceeded for 3 days at 60° C Thick epon sections (0 5 to 1 0 micron) were cut and stained with toluidine blue in order to ascertain the plane of orientation for selection of the areas to be subsequently sectioned for electron microscopy Thin sections (500 to 600 Å) from these areas were stained with lead citrate and uranyl acetate and were examined with a Siemens Elmiskop I microscope

In order to make certain which layer of the aorta was being viewed with the electron microscope when scanning from one layer of the aorta to the next the tissue blocks were carefully trimmed to specific layers After thin sections were made from these blocks an adjacent thick section was prepared to verify that the blocks were limited to the prescribed layers The thin sections were scanned using the luminal surface as a reference point thereby estimating the location of a particular cell or cellular layer from that surface The intimal medial and adventitial layers were sectioned in this fashion In addition areas were trimmed in which there were no specific pathologic features The whitish spots observed grossly could not be dis

Results

Immunofluorescent observations Positive immunofluorescent staining for Coxsackie B_4 virus antigen was found in the cytoplasm of fibroblasts of the adventitia of the aorta (Fig 2) This positive immunofluorescent staining was blocked by unlabelled Coxsackie B_4 virus antibody

Histologic observations Microscopic observations of the aortic intima media and adventitia revealed slight to moderate alterations in the intima and adventitia and slight changes in the media The endothelial cells were abnormal or were absent in all sections The intima was fibrotic and contained fat droplets (Fig 3) In some areas the intima was slightly thickened Fibroblastic proliferation was present in the subendothelial areas near the lumen of the aorta The interstices between the proliferating fibroblasts appeared edematous being pale basophilic and with loosely connected ground substance In the middle of the thickened intima fat droplets were accumulated and the outermost layer of the intima near the media was fibrotic Cells with small dense basophilic nuclei were scattered throughout the intima indicating a slight degree of inflammatory cell infiltration

Interstitial edema represented by clear interspaces between the elastic lamellae and smooth muscle cells associated with

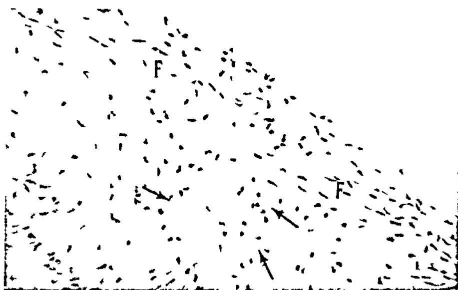


Fig. 7 Photomicrograph of a portion of the thickened intima of the aorta of the 19 year old patient who died of Coxsackie B_4 viral infection. The innermost portion shows fibroblastic proliferation (*F*) in an edematous background. Fat droplets (*arrows*) accumulated within the intima. The outermost portion of the intima is more densely fibrotic than the inner portion. Small dense basophilic nucleated cells, probably inflammatory cells, are scattered throughout the intima. (Hematoxylin and eosin. Original magnification ×100.)

buffered saline, the sections were stained with fluorescein labelled rabbit antiserum to Coxsackie B_4 virus for 45 minutes in a high humidity chamber. They were then washed again in phosphate buffered saline. The tissues were examined with Gillett Sibert and Reichert UV microscopes.

The antiserum was prepared by infecting rabbits with 0.4 ml. Coxsackie virus B_4 antigen intramuscularly and 0.1 ml. in the foot pad once a week for 3 weeks. The antigen was obtained by conjugating the purified Coxsackie virus with methylated bovine serum albumin and adding complete Freund's adjuvant.[8] The rabbits were bled after 3 weeks by cardiac puncture and the serum samples titered. The rabbits were injected once more and exsanguinated one week later. Serum samples were fractionated on a DEAE cellulose ion exchange column and 0.05 molar phosphate buffer (pH 8.0) were collected and labelled with 12.5 micrograms of FITC per milligram of protein in a 10 per cent sodium carbonate bicarbonate buffer (pH 9.5) in a cold environment for 4 hours and then dialyzed against starting buffer with activated charcoal added. Acetone dried tissue powder was used to absorb excess fluorescein and nonspecific antibody prior to staining the tissue sections.

Some sections were tested for immunofluorescent blocking by staining the sections first with unlabelled Coxsackie virus B_4 antibody and then with labelled antibody.

Histologic method. Aortic tissue was fixed in 10 per cent neutral formalin, dehydrated and embedded in paraffin. Sections, 7 microns thick, were stained by a routine hematoxylin and eosin method and were examined with a light microscope.

Electron microscopic method. Pieces of tissue approximately 1.5 mm. by 6 mm. long, cut through the entire thickness of the aorta, were placed in cold 3 per cent glutaraldehyde in phosphate buffer (pH 7.3) for 2 hours. The tissues were subsequently rinsed in 6 changes of fresh phosphate buffer with sucrose (pH 7.3) at 30 minute intervals and were left overnight in cold buffer. Post fixation was with cold 1 per cent osmium tetroxide in phosphate buffer for 1.5 hours. Dehydration was initiated in a graded series of cold methanol and completed with three changes of pure methanol (20 minutes each) at room temperature. Infiltration was accomplished with pure propylene oxide. The tissues were transferred to fresh vials containing a mixture of ½ propylene oxide and ½ epon and were placed under a lamp overnight. Impregnation with epon was completed with 2 changes of pure epon for 1

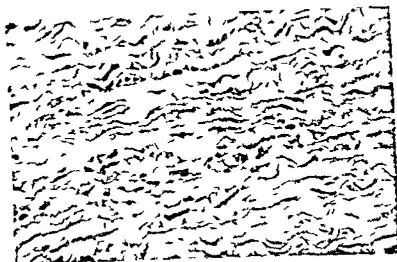


Fig 4 Photomicrograph of the media of the aorta of the 19 year old patient with Coxsackie B_4 viral infection Inter titial edema is associated with di placement of the elastic lamellae and smooth muscle cell (Hema toxylin and eosi n Orig nal magnification ×200)

hour each The tissues were embedded in flat molds with appropriate orientation Polymerization proceeded for 3 days at 60° C Thick epon sections (0 5 to 1 0 micron) were cut and stained with toluidine blue in order to ascertain the plane of orientation for selection of the areas to be subsequently sectioned for electron mi croscopy Thin sections (500 to 600 Å) from these areas were stained with lead citrate and uranyl acetate and were ex amined with a Siemens Elmiskop I micro scope

In order to make certain which layer of the aorta was being viewed with the elec tron microscope when scanning from one layer of the aorta to the next the tissue blocks were carefully trimmed to specific layers After thin sections were made from these blocks an adjacent thick section was prepared to verify that the blocks were limited to the prescribed layers The thin sections were scanned using the luminal surface as a reference point thereby esti mating the location of a particular cell or cellular layer from that surface The inti mal medial and adventitial layers were sectioned in this fashion In addition areas were trimmed in which there were no specific pathologic features The whitish spots observed grossly could not be dis tinguished in the toluidine blue sec

Results

Immunofluorescent observations Positive immunofluorescent staining for Coxsackie B_4 virus antigen was found in the cyto plasm of fibroblasts of the adventitia of the aorta (Fig 2) This positive immunofluores cent staining was blocked by unlabelled Coxsackie B_4 virus antibody

Histologic observations Microscopic ob servations of the aortic intima media and adventitia revealed slight to moderate alterations in the intima and adventitia and slight changes in the media The endo thelial cells were abnormal or were absent in all sections The intima was fibrotic and contained fat droplets (Fig 3) In some areas the intima was slightly thickened Fibroblastic proliferation was present in the subendothelial areas near the lumen of the aorta The interstices bet een the proliferating fibroblasts appeared edema tous being pale basophilic and with loo ely connected ground substance In the middle of the thickened intima fat droplets were accumulated and the outermost layer of the intima near the media was fibrotic Cells with small dense basophilic nuclei were scattered throughout the intima indi cating a light degree of inflammatory cell infiltration

Interstitial edema represented by clear interspaces between the elastic lamellae and smooth muscle cells associated with

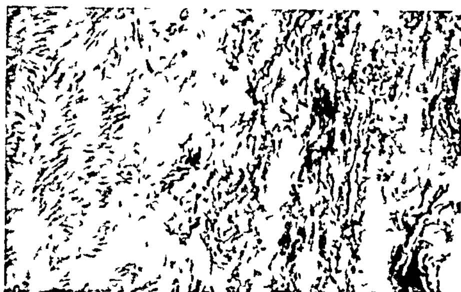


Fig. 5 Photomicrograph showing collagenous tissue proliferation and interstitial hemorrhage in the adventitia of the aorta of the patient (Hematoxylin and eosin Original magnification ×100.)



Fig. 6 Photomicrograph of the adventitia of the aorta of the patient The number of small blood vessels in the adventitia is increased Collagenous tissue proliferation and interstitial hemorrhage are also present (Hematoxylin and eosin Original magnification ×100.)

disruption of these components was found in some areas of the media (Fig 4) Proliferation of collagenous tissue was observed in the adventitia (Fig 5) Interstitial hemorrhage was widespread and varied in severity (Figs 5 and 6) and the number of small blood vessels in the adventitia was increased (Fig 6) These changes are indicative of inflammation

Electron microscopic observations The endothelial lining of the aorta was absent This was possibly due to the preparation of the tissue, but the lining may also have been absent prior to the initiation of tissue preparation in which case it can be speculated that it was pathologically altered and destroyed In addition there was no organized subendothelial layer Since no significant alterations were apparent in the media or adventitia by electron microscopy the description of the electron microscopic findings will be limited to the intima of the aorta

The intima was thickened with the cells scattered and separated by bundles of collagen and widened extracellular spaces Many of the cells of the intima contained within their cytoplasm varying

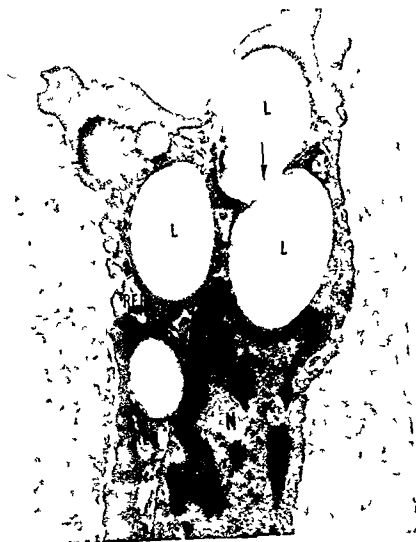


Fig. 7 Electron micrograph of the aortic intima of the patient showing lipid droplets (*L*) within the cytoplasm of a fibroblast. Two of the droplets have coalesced (*arrow*). The end of the nucleus (*N*) is indented by one of the droplets. Cisternae of rough endoplasmic reticulum (*RER*) are apparent. (Original magnification × 37 000.)

numbers of lipid droplets which measured 1.0 to 5.0 microns in diameter (Fig. 7). In many instances the droplets were coalesced with other droplets often forming chains. Three cell types were observed in which lipid had accumulated. However, in some cells the cytoplasm was so full of lipid that the cell type could not be identified with certainty (Fig. 8). The innermost area of the intima closest to the lumen consisted mostly of fibroblast-like cells. However, many of the cellular components encountered were so small and fragmentary that their cell type could not be ascertained.

Deeper into the intima approaching the medial layer most of the cells were relatively large smooth muscle cells. Occasionally cells considered to be macrophages were encountered. There was no clearly definable mononuclear infiltration.

Lipid appeared to be deposited mostly in fibroblast-like cells; however, the less numerous macrophages contained more lipid per cell. Smooth muscle cells were most frequently devoid of lipid, especially those deeper within the intima. However, some smooth muscle cells had 1 or 2 lipid

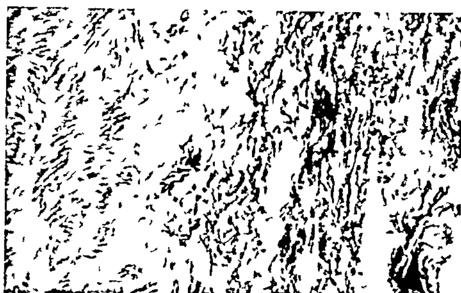


Fig. 5. Photomicrograph showing collagenous tissue proliferation and interstitial hemorrhage in the adventitia of the aorta of the patient. (Hematoxylin and eosin. Original magnification ×100.)



Fig. 6. Photomicrograph of the adventitia of the aorta of the patient. The number of small blood vessels in the adventitia is increased. Collagenous tissue proliferation and interstitial hemorrhage are also present. (Hematoxylin and eosin. Original magnification ×100.)

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Electron microscopic observations. The endothelial lining of the aorta was absent. This was possibly due to the preparation of the tissue, but the lining may also have been absent prior to the initiation of tissue preparation, in which case it can be speculated that it was pathologically altered and destroyed. In addition, there was no organized subendothelial layer. Since no significant alterations were apparent in the media or adventitia by electron microscopy, the description of the electron microscopic findings will be limited to the intima of the aorta.

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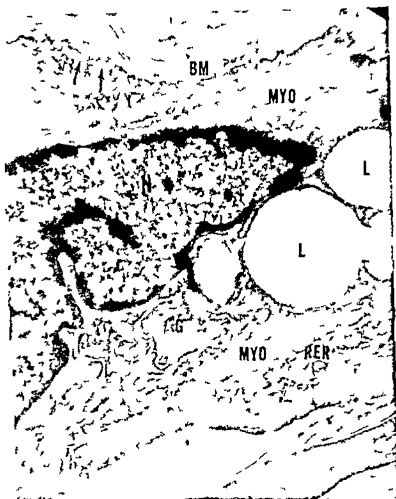


Fig 9 Electron micrograph of a portion of a smooth muscle cell from the patient s aortic intima The cell is characterized by the presence of myofilaments (*MYO*) a basement membrane (*BM*) and pinocytotic vesicles (*arrows*) The nucleu (*N*) w th peripheral chromat n is centrally located Lipid droplets (*L*) are present in the cytopla m A Golgi apparatus of several laminate cisternae (*G*) can be seen close to the nucleus Elements of the rough endopla mic reticulum (*RER*) are also present (Original magnification X27 000)

filaments within the cytoplasm presence of pinocytotic vesicles and presence of a surrounding basement membrane The smooth muscle cells had a well-developed Golgi apparatus Rough endoplasmic re ticulum was common though not abun dant Most of the smooth muscle cells had only one or two small lipid droplets or were without lipid Occasionally a cell was encountered in which several lipid droplets were apparent (Fig 9)

The third type of cell in which lipid was found was considered to be a macrophage (Fig 8) This cell may also represent the foam cell previously described in aortic fatty streaks[6,7] In the cell illustrated in Fig 8 the nucleus was displaced to one side by the large amount of accumulated lipid The cytoplasm was condensed in areas as a result of crowding by the lipid Coalescence of lipid droplets was a common observation Mitochondria were scarce and rough endoplasmic reticulum was sparce Occasional dense bodies which are possibly cytolysomes were seen Vesicles smaller than the lipid droplets and with electron dense contents were also seen Small thin projections of the cytoplasm, which protruded into the extracellular space were frequently observed in these

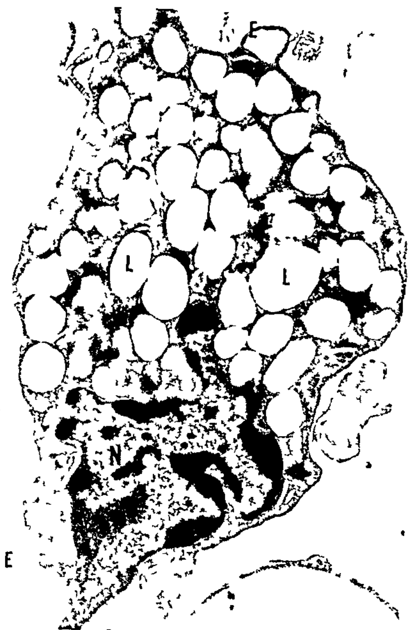


Fig 8 Electron micrograph of a macrophage from the intima of the patient's aorta The cytoplasm contains an abundance of lipid droplets of various sizes (*L*) The nucleus (*N*) is displaced to one side by crowding of lipid The cytoplasm is dense due to compression Small thin protoplasmic extensions (*E*) protrude from the cell periphery (Original magnification ×21 600)

droplets, and a few had more than 2 droplets (Fig 9)

The fibroblast like cells (Fig 7) were identified by their elongated profile and irregular projections into the extracellular space, absence of myofilaments and absence of a surrounding basement membrane The cell demonstrated in Fig 7 represents a protoplasmic extension of a fibroblast containing several lipid droplets The cytoplasm is homogeneously dense The nucleus is elongated, with peripheral chromatin Short profiles of rough endoplasmic reticulum can be seen Pinocytotic vesicles were not apparent Thin fibrils arranged loosely into small bundles were found within the extracellular spaces Extracellular fibrous material was observed in close apposition to the plasma membrane

The smooth muscle cells were generally larger than the fibroblast like cells and were disposed more frequently near the media The smooth muscle cells (Fig 9) were distinguishable from the fibroblast like cells (Fig 7) by the presence of myo

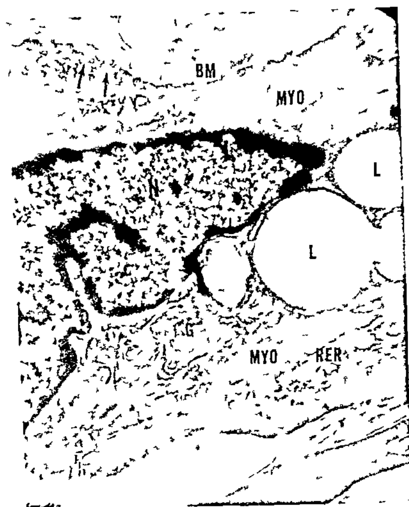


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cells The macrophage clearly lacked a basement membrane

Discussion

The alterations observed in this patient are indicative of inflammation of the aorta These include thickening fibroblastic proliferation fibrosis and basophilic infiltration of the intima, edema of the media, accumulation of lipid proliferation of collagenous tissue, hemorrhage and increased vascularization in the adventitia The important finding of fairly extensive fat deposition within the intima is suggestive of atherosclerotic changes in this young man who died of a viral infection Furthermore immunofluorescent antibody staining was positive for Coxsackie B_4 virus in cells of the aorta Because of the young age of this patient (19 years) the possibility that the lipid deposition resulted only from a progressive aging phenomenon is unlikely Also from the clinical data it is unlikely that the lipid deposits were due to either hypertension or to a high cholesterol diet in this patient

Aortitis indicated by inflammatory changes in the aortic wall has been observed in syphilis[9] rheumatic fever[10] rheumatoid arthritis[11] and pulseless disease[12] or aortitis syndrome[13] Fibrous thickening of the intima and the adventitia and disruption and loss of elastic and muscular fibers in the media are the common morphologic alterations of the aortic wall in these diseases

Lipid deposition on the other hand which has been considered an early manifestation of atherosclerotic lesions[7] and which is usually not observed in vasculitis was observed in this patient It is evident, therefore that there were changes in the aorta associated with early atherosclerotic changes It is not possible to decide from our present data which of these changes occurred first But, when it is realized that this patient was young and that immunofluorescent antibody staining for Coxsackie B_4 virus antigen was positive in the aorta it should be considered that a viral infection of the aorta at least might have predisposed to the lipid deposition Deposition of lipid in injured tissue can occur extremely rapidly in a few hours to a few days The fact that positive immunofluorescent antibody staining for antigen of Coxsackie virus B_4 was observed in the cells of the adventitia of the aorta of this patient suggests the possibility that the inflammatory changes in the aortic wall were caused by viral infection Upon examination with the electron microscope, it was found that most of the intimal cells contained lipid in varying quantities However no extracellular lipid which has been considered an early manifestation of the formation of atherosclerotic lesions,[7] was found

Most of the lipid containing cells could be recognized as fibroblast like cells They were usually closest to the luminal surface of the aorta Lipid containing smooth muscle cells were more frequently encountered and lipid containing fibroblasts were less frequently encountered in areas progressively more distal to the luminal surface The smooth muscle cells became increasingly surrounded by elastin fibers in the more distal regions Many of the deeper smooth muscle cells were without lipid, although, as indicated above, some contained 1 or 2 droplets and a few contained numerous droplets of lipid These observations are contrary to earlier reports[4, 7] of atherosclerotic lesions both proliferative lesions (non necrotic) and fatty streaks In those reports the predominant cells were mature smooth muscle cells and the lipid laden cells were either monocytes[4] smooth muscle cells[6] macrophages[6] or foam cells[5, 7] Only a few cells which could be considered as either macrophages or foam cells were encountered in the aorta of the patient described here No cells could be recognized as monocytes

In man fat droplets appear in smooth muscle cells at an early stage in the formation of atherosclerotic lesions[14] As the accumulation of fat continues the smooth muscle cells develop into myogenic foam cells[14] The foam cells subsequently degenerate and empty their contents into the extracellular space This fat in turn, is phagocytosed by macrophages which in time may assume the features of foam cells[14] In a recent report it was indicated that some foam cells may be derived from smooth muscle cells whereas others, which resemble macrophages appear to be derived from monocytes previously circulating in the blood stream[6] It has not been

stablished whether the macrophages are ltered primitive cells which migrate from he aortic media or whether they are de rived from the circulating blood and gain entrance into the intima after migrating through the endothelial lining of the aorta

It should be pointed out that lesions com patible with early atherosclerotic changes have been described in our patient It is proposed that the changes reported in this patient were a result directly or indirectly of the accompanying Coxsackie B_4 viral infection It seems possible that injury to the arterial vessels by a viral agent could be one of the factors which initiate a site of injury which through time arterial blood pres ure and lipoproteins and cho lesterol circulating in the blood is repaired resulting in the formation of scars and other atherosclerotic changes observed in all people especially later in life Arterio sclerosis has a beginning it starts in young people and accumulates other injuries with time to become more extensive with age Viremia with viral injury of the ar terial system must be seriously considered as an initiating factor of atherosclerosis Viral infections begin with life and con tinue throughout life We have shown in previous studies in experimental animals that viruses can injure extensively the aorta coronary arteries and other arteries of mice[15,16] It is our contention th t atherosclerosis and arterio clerosis with calcification and ulceration are late scars and reparative phenomena of earlier and more fundamental lesions of the arterial vessels[17] This concept would also explain the reasons for the particular sites of the atherosclerotic and arteriosclerotic lesions noted by pathologists and clinicians

Summary

A 19 year old young man who died of viral cardiomyopathy had positive staining of the myocardium kidney pancreas and aorta with immunofluorescent antibodies for Coxsackie B_4 virus The aorta was found to have an accumulation of lipid material in cells of the intima The lipid deposits were located electron microscopically in fibroblasts smooth muscle cells and macro phages It is suggested that viral infections so common in man may produce local sites [illegible] result in the scars and lipid calcium and other deposits which represent the well known lesions of atherosclerosis and arteriosclerosis These scars and late lesions must have a begin ning and from the manifestations of immunofluorescent antibodies histopatho logic and electron microscopic findings in the aorta of the patient described here as well as from the clinical data it is suggested that Coxsackie B_4 virus may initiate atherosclerosis and arteriosclerosis in man

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Charcot-Marie-Tooth disease, Wolff-Parkinson-White syndrome, and abnormal intracardiac conduction

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This report describes the occurrence of the Wolff-Parkinson-White syndrome (anomalous atrioventricular excitation and recurrent paroxysmal tachycardia) in a young man with Charcot-Marie-Tooth disease (peroneal muscular atrophy). In addition to the fascinating compounding of eponyms, this patient is of interest because his electrocardiograms on occasion showed delayed conduction from the sino-auricular node to the ventricles both via the normal path and via the accessory path, and also left anterior fascicular block.

Case report

This Canadian-born white male had been known to have paroxysmal supraventricular tachycardia (Fig. 1) since early life with intermittent normal ventricular excitation (Fig. 2) and intermittent anomalous ventricular excitation (Fig. 3).

At the age of 22 years he was noted to display the features of peroneal muscular atrophy, namely wasting of the distal muscles of the extremities, high arched feet, and curled toes. The conduction velocity along his left median nerve was measured at 49 meters per second and along his left ulnar nerve at 53 meters per second; these values are at the lower limit of normal and are quite unusual for a healthy young man.

The patient's electrocardiograms intermittently showed delayed atrioventricular conduction both by the accessory path (Figs. 3 and 4) and by the normal path (Fig. 4). The atrioventricular conduction delay occurred in the absence of digitalis administration and was not modified by the assumption of the upright posture or by the intravenous administration of atropine 1.2 mg. The patient's electrocardiograms also showed left anterior fascicular block.

There was no knowledge of the occurrence of the Wolff-Parkinson-White syndrome or of Charcot-Marie-Tooth disease in other members of his family. His parents, his three younger brothers, and his only sister were examined for clinical evidence of peroneal muscular atrophy. No evidence of this disorder was found. Because his siblings ranged in age from 10 to 21 years when examined, it remains possible that they may manifest the stigmata of peroneal muscular atrophy in the future. Electrocardiograms from his parents and four siblings showed no conduction abnormalities or tachyarrhythmias. Because the Wolff-Parkinson-White phenomenon is commonly intermittent, these normal electrocardiograms do not exclude the possibility of intermittent anomalous atrioventricular excitation in these other members of his family.

Discussion

This patient displayed the classical clinical features of peroneal muscular atrophy; the diagnosis was supported by the slow rate of conduction along his peripheral nerves. He displayed also the classical clinical features of the Wolff-Parkinson-White syndrome, namely anomalous atrioventricular excitation and recurrent paroxysmal supraventricular tachycardia. His electrocardiograms were unusual in that impulses conducted to the ventricles both by the normal path and by an accessory path at times showed prolonged atrioven-

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Fig 1 Regular supraventricular tachycardia with ventricular rate approximately 187 per minute

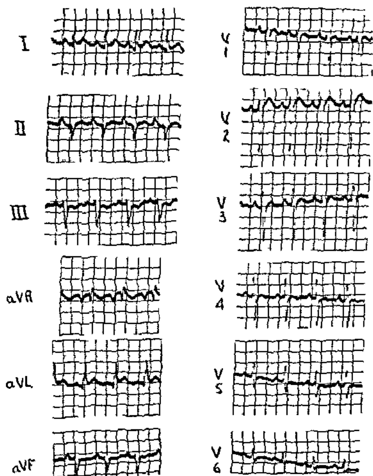


Fig 2 Sinus rhythm with atrioventricular conduction via the normal path (PR interval = 0 20 sec) The QRS complexes are similar to those in Fig *1* indicating that during that paroxysm of supraventricular tachycardia ventricular excitation occurred via the normal path Note also the left anterior fascicular block

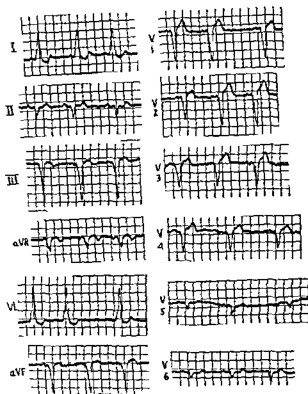


Fig 3 Sinus arrhythmia with anomalous atrioventricular excitation The P delta intervals vary from 0 15 to 0 21 second in duration According to the criteria of Rosenbaum and associates [3] this electrocardiogram is an example of the Wolff Parkinson White syndrome (Type B) Bruyneel[4] has proposed that the initial delta vector be the criterion for the electrocardiographic subdivision of the W P W syndrome regardless of the duration and sense of the main QRS vector—a positive delta wave in Lead V_1 indicating Type A and a negative delta wave in Lead V_1 indicating Type B If this criterion is employed this electrocardiogram must be classed as an example of the W P W syndrome (Type A)

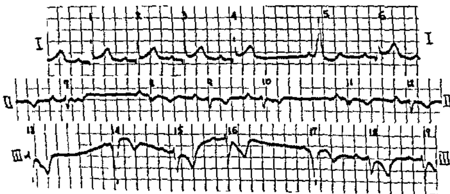


Fig 4 Intermittent anomalous atrioventricular excitation with delayed AV conduction both by the normal path (P Q = 0 24 second) and via the accessory route (P delta = 0 17 second) In complexes 7 10 13 and 16 there are thought to be retrograde premature P[1] waves caused by re entry of impulses into the atria in retrograde direction via the accessory atrioventricular path Because the P[1] waves are negative in Leads II and III Wolff Parkinson White syndrome Type A (resulting from a bypass connecting the left atrium and left ventricle) is suggested[7] Note that the intermittent single anomalous atrioventricular excitation complexes (5 8 11 14 and 17) occur after long P-P intervals presumably due to resetting of the SA node by the retrograde P waves. The absence of delta waves after shorter P-P intervals suggests that the refractory period of the accessory path is longer than that of the normal path

Table I. Reported patients with peroneal muscular atrophy and abnormal intracardiac conduction

Author	*Patient*	*Peroneal muscular atrophy*	*AV conduction abnormality*	*Intraventricular conduction abnormality*	*Arrhythmia*
Legrand et al[1]	Male aged 44	Variant	PR = 0.30 sec	Left bundle branch block	None
Leak[2]	Male aged 59	Typical	Varying AV block in association with atrial flutter	None	Atrial flutter
Littler[3]	II 1 male aged 41	Typical	Complete AV block with Stokes-Adams attacks	Previous ECG showed right bundle branch block and left axis deviation	None
	I 2 male aged 74	Bilateral pes cavus	None	Right bundle branch block and left axis deviation	None
	II 2 female aged 40	Bilateral pes cavus	None	Incomplete right bundle branch block	None
Kay et al[4]	Same patient as Littler[3] II 1				
Present report	Male aged [illegible]	Typical	Intermittent first degree AV block	Left anterior fascicular block	W P W syndrome (type A) paroxysmal supraventricular tachycardia

tricular conduction and also left anterior fascicular block.

It is tempting to speculate regarding the significance of intracardiac conduction disturbances in patients with peroneal muscular atrophy. The possibility that this association is merely coincidental seems unlikely in view of the increasing number of patients in whom this association has been recognized (Table I). Littler[3] has reviewed in detail possible genetic explanations which might account for the association of cardiac conduction defects and peroneal muscular atrophy in the family he reported. Surely, the possibility must also be considered that the prolonged peripheral nerve conduction and prolonged intracardiac conduction in these patients have a common etiology: although peripheral nerve conduction is based on nerve cells and cardiac conduction on specialized myocardial cells, this anatomic difference need not imply a physiologic difference in the electrochemical transmission of impulses via specialized myocardial cells as opposed to nerve cells.

Summary

A patient with Charcot-Marie-Tooth disease, Wolff-Parkinson-White syndrome and abnormal intracardiac conduction has been reported.

The peripheral nerve conduction velocity studies were carried out by Dr. W. St. J. Buckler, Vancouver, B. C., Canada. The author is grateful to Dr. F. C. MacInnes, Summerland, B. C., Canada, for referring this patient and to Dr. Alfred Pick of Michael Reese Hospital, Chicago, Illinois, for his comments on the patient's electrocardiograms.

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Chicago Ill

Case history

C Y a 25 year old Japanese man was admitted for the fifth and last time to Michael Reese Hospital because of shortness of breath

In 1950 at the age of four the patient was first given a diagnosis of systemic lupus erythematosus (LE) at Children's Memorial Hospital and was started on steroids In 1956 he underwent bilateral iridectomies because of cataracts and glaucoma In 1960 he was noted to develop generalized osteoporosis with compression fractures of the vertebral bodies and aseptic necrosis of the left talus over a period of two years These complications were attributed to steroids which were discontinued in 1962 In April 1965 at the University of Illinois a renal biopsy was done for the first time and showed moderately severe diffuse membranous glomerulonephritis without vascular or proliferative changes He was treated with azathioprine at this time and was continued on this for two to three years when his disease was thought to be inactive He was followed in the clinic and was described as having done quite well being active both at work and in school

In August 1969 he was first admitted here with the acute onset of right sided flank pains and lower limb swelling following a four hour automobile trip Phlebograms confirmed the presence of inferior vena cava obstruction at the level of the fourth lumbar vertebra clots were also found in the left femoral left external iliac and common femoral veins The patient was treated with bishydroxycoumarin Upon discharge heavy proteinuria continued with evidence of lupus activity

He was readmitted a second time in November 1969 At this time there was evidence of lupus with positive LE preparations positive antinuclear antibodies B C complement of 55 (range 145 ± 22) presence of cryoglobulin active sediment with 50 RBCs (red blood cells) 30 WBCs (white blood cells) per high power field with doubly refractile oval fat bodies and 1 014 Gm of proteinuria in 24 hours The BUN (blood urea nitrogen) was 40 with a creatinine of 1 1 mg per 100 ml A renal biopsy was done revealing active lupus and compared to the 1965 biopsy revealed more focal and segmental proliferative and sclerosing features with occasional crescent formation Inferior vena cavagram revealed partial recanalization and Coumadin was continued To treat the active lupus a course of nitrogen mustard was given and the patient was begun on prednisone 25 mg daily The cholesterol was then 340 mg per 100 ml and albumin 2 1 mg per 100 ml

In April 1971 the patient was admitted for the fourth time with an acute myocardial infarction complicated by multifocal ventricular premature beats and congestive heart failure requiring lidocaine digitalis and quinidine therapy At this time he was also found to have hyperlipidemia with Type II electrophoretic pattern with cholesterol of 280 a low cholesterol diet was begun Other laboratory data included an albumin of 1 9 Gm *per cent urinalysis revealed active sediment oval* fat bodies and 3 8 Gm proteinuria during 24 hours LE preparations were negative three times and B C complement was normal twice Coumadin which the patient had stopped taking before admission

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Table I. Reported patients with peroneal muscular atrophy and abnormal intracardiac conduction

Author	Patient	Peroneal muscular atrophy	AV conduction abnormality	Intraventricular conduction abnormality	Arrhythmia
Legrand et al.[1]	Male aged 41	Variant	PR = 0.30 sec	Left bundle branch block	None
Leak[2]	Male aged 39	Typical	Varying AV block in association with atrial flutter	None	Atrial flutter
Littler[3]	II 1 male aged 41	Typical	Complete AV block with Stokes-Adams attacks	Previous ECG showed right bundle branch block and left axis deviation	None
	I 2 male aged 74	Bilateral pes cavus	None	Right bundle branch block and left axis deviation	None
	II 2 female aged 40	Bilateral pes cavus	None	Incomplete right bundle branch block	None
Kay et al.[4]	Same patient as Littler[3] II 1				
Present report	Male aged 29	Typical	Intermittent first degree AV block	Left anterior fascicular block	W-P-W syndrome (type A); paroxysmal supraventricular tachycardia

tricular conduction and also left anterior fascicular block.

It is tempting to speculate regarding the significance of intracardiac conduction disturbances in patients with peroneal muscular atrophy. The possibility that this association is merely coincidental seems unlikely in view of the increasing number of patients in whom this association has been recognized (Table I). Littler[3] has reviewed in detail possible genetic explanations which might account for the association of cardiac conduction defects and peroneal muscular atrophy in the family he reported. Surely the possibility must also be considered that the prolonged peripheral nerve conduction and prolonged intracardiac conduction in these patients have a common etiology. Although peripheral nerve conduction is based on nerve cells and cardiac conduction on specialized myocardial cells, this anatomic difference need not imply a physiologic difference in the electrochemical transmission of impulses via specialized myocardial cells as opposed to nerve cells.

Summary

A patient with Charcot-Marie-Tooth disease, Wolff-Parkinson-White syndrome and abnormal intracardiac conduction has been reported.

The peripheral nerve conduction velocity studies were carried out by Dr. W. St. J. Buckler, Vancouver, B. C., Canada. The author is grateful to Dr. F. C. MacInnes, Summerland, B. C., Canada, for referring this patient, and to Dr. Alfred Pick of Michael Reese Hospital, Chicago, Illinois, for his comments on the patient's electrocardiogram.

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though serial ECGs and enzymes were not diagnostic. Five days later the patient was discharged from the coronary surveillance unit. On the seventeenth hospital day, seven days after the presumed infarct, a pericardial friction rub was heard with a low grade fever which then disappeared spontaneously. On the twenty-fifth hospital day a holosystolic murmur was first heard in the apex with radiation to the axilla. The heart tones were noted to be muffled and distant. The patient, however, was improving clinically. There was no evidence of congestive heart failure and chest pains were less frequent, although the ECGs continued to show a possible active myocardial or pericardial process. On the tenth and twenty-first hospital days LE preparations were positive and on the thirtieth hospital day the BUN was 72 mg per 100 ml. On the twenty-fifth hospital day azathioprine was started because of the possible activity of the disease and in an effort to be able to reduce the steroid dose of 30 mg prednisone daily. By the thirtieth hospital day the patient was completely asymptomatic. The renal status was stable and he was gradually ambulating without any problems. On the thirty-third hospital day the patient was discharged.

Two days after discharge from the hospital the patient died.

Discussion

DR. IZZY SOMMERS (MODERATOR). The case for discussion today is that of a 25-year-old man who presented with systemic lupus erythematosus (SLE) and the nephrotic syndrome. We are privileged to have with us to solve the problems of this case Dr. Norman M. Simon, Associate Professor of Medicine at Northwestern University Medical School.

DR. N. M. SIMON. The case presents an unusual challenge in that the diagnosis of SLE appears to be well established. The course is an extended one and my task is to sort out the nature and extent of the systems involved by the SLE process and to determine whether other significant diseases also were present.

The patient was a 25-year-old Japanese man. In our experience at Northwestern University Medical Center we have noted an increased prevalence of people of the Oriental race in patients with SLE.[1] He was found to have SLE at the age of 4 years and was started on corticosteroid therapy. Two years later he first showed renal involvement manifested by the nephrotic syndrome. Subsequently he developed a number of serious complications related to steroids which were discontinued after a treatment period of eight years. The first renal biopsy was performed nine years after the onset of renal disease and the tissue was reported to show diffuse membranous glomerulonephritis. This is one type of renal lesion found in SLE. Involvement of the kidneys is common in lupus, occurring in 50 to 80 per cent of patients, generally early in the clinical course. The renal lesions of SLE have been well defined by Pollak and Pirani[2] and Baldwin and co-workers.[3] In addition to membranous glomerulonephritis these include a mild alteration labeled as minimal glomerular involvement or focal glomerulonephritis and a severe abnormality described as active or diffuse glomerulonephritis. Each lesion appears to have its own natural history and there is little tendency for one to progress into another.

The patient was then started on treatment with azathioprine which was continued for several years until the disease was inactive. He returned a year or two later with signs of acute occlusion of the major veins of the left leg extending into the inferior vena cava. The occurrence of right flank pain suggests involvement of the renal veins as well, which might account for the observed increase in proteinuria. Indeed, it is possible that renal vein thrombosis may have been the underlying disorder from the very beginning. The renal biopsy finding of membranous glomerular changes is compatible with this speculation.

However, there are alternative explanations to account for thrombotic venous disease in this patient. First, SLE is a vasculitis which may affect veins as well as arteries. Second, significant abnormalities in blood coagulation are found in patients with the nephrotic syndrome regardless of etiology.[4] These include increased levels of plasma fibrinogen, factors V, combined VII and X, VIII, and platelets and accelerated thromboplastin generation. The coagulation abnormalities disappear as the nephrotic syndrome goes into remission. As infection formerly was a major threat to nephrotic patients before the introduction of antibiotics, thromboembolism now stands as a serious complication of their disease.

The patient was started on treatment with oral anticoagulants but required readmission to the hospital a short time later with evidence of active disease. A large

was reinstituted and prednisone was continued at 30 mg daily Coumadin prednisone and quinidine were continued after discharge

In July 1971 he was admitted for the fifth and last time with a two-day history of progressive shortness of breath increasing leg swelling fever tachycardia and coughing He denied any chest pain or hemoptysis and there was no abnormal bleeding His cough was productive of whitish sputum He also complained of pain in his testicles for about three days

Physical examination on admission The patient appeared Cushingnoid and was in moderate respiratory distress Vital signs included blood pressure of 116/80 mm Hg pulse 110 per minute with occasional premature beats respirations 40 per minute and labored and temperature was 102° F The skin was warm with good turgor There was a dry scaly slightly red maculopapular rash over the face with butterfly distribution and well delineated borders similar lesions appeared on the dorsum of both hands and in the groin areas with strikingly well delineated borders Acneiform eruptions were present in the neck chest and back The head was normocephalic The eyes showed bilateral iridectomy scars and absent left lens The fundi showed flat discs with arteriolar narrowing and A V nicking no hemorrhages exudates or cytoid bodies were seen The neck was supple with moderate jugular venous distention at 45° The hepatojugular reflux was positive The chest expanded symmetrically without splinting there was diffuse wheezing with bilateral basilar râles There was no evidence of consolidation or effusion The point of maximum cardiac impulse was not palpable or visible The heart tones were of good quality S_1 and S_2 were normal S_3 was intermittently heard at the apex and S_4 was present No murmurs or rubs were heard The abdomen was distended no fluid waves could be elicited There were numerous venous collaterals seen on the abdominal wall The liver span was 12 cm with a smooth nontender edge The spleen was not felt There was bilateral pedal edema There was no evidence of thrombophlebitis Homan s sign was negative There was no clubbing The nails were pink white and scaly The right epididymis was markedly swollen and inflamed and extremely tender to palpation The neurological examination revealed no abnormalities

Laboratory data The hemoglobin was 14 5 Gm per cent hematocrit 44 7 per cent and RBC count 4 5 million per cubic millimeter WBC count was 8 600 per cubic millimeter with a differential of 78 neutrophils 1 band 15 lymphocytes 6 monocytes and numerous platelets Urinalysis showed a pH of 6 specific gravity 1 005 a large amount of protein and negative for sugar and acetone There were seven to fifteen RBC s and two to five WBC s per high power field Also the urinalysis showed a few bacteria and was positive for doubly refractile fat bodies The chest x ray showed cardiomegaly with pulmonary vascular congestion An ECG (electrocardiogram) showed old posteroinferior myocardial infarction with frequent PVC s (premature ventricular contractions) Sodium was 148 potassium 4 3 chloride 95 and CO_2 23 mEq per liter BUN was 42 creatinine 1 7 mg per cent The arterial blood gases showed a pH of 7 48 a Pco_2 of 26 and a Po_2 of 139 mm Hg while the patient was receiving oxygen by nasal cannula The SGOT (serum glutamic oxalacetic transaminase) was 35 SGPT (serum glutamic pyruvic transaminase) 42 LDH (lactic dehydrogenase) 357 CPK (creatine phosphokinase) 7 units Serial examinations of these enzymes did not show any significant increase The alkaline phosphatase was 2 5 Bodansky units The total bilirubin was 0 3 direct 0 2 mg per 100 ml Total protein was 5 3 Gm per cent with albumin of 2 4 Gm The serum cholesterol was 220 and triglycerides 89 mg per 100 ml Serum complement done on July 23 1971 was 80 mg per 100 ml on July 29 1971 120 mg per 100 ml The IgG was 1 000 IgA 210 IgM 350 mg per 100 ml Cryoglobulin was present A 24 hour urine protein showed 2 23 Gm per 24 hours The RA factor was negative The first two L E preparations were negative but later these became positive The prothrombin time was 22 8 seconds PTT was 46 6 seconds with a control of 39 0 Blood and sputum cultures for acid fast bacilli were negative A urine culture was also negative as well as stool cultures Skin lesions on the face hands and groin showed mycelium and spores on the potassium hydroxide smears

Hospital course The patient was extremely anxious and acutely short of breath He was thought to be in congestive heart failure and treatment was begun with diuretics digitalis and sedation with good response The possibility of pulmonary embolization was strongly suspected heparin therapy was started An emergency lung scan showed evidence only of pulmonary congestion and other nonspecific findings Cardiologic and cardiovascular consultation suggested that conservative management without further diagnostic studies was indicated By evening the patient had markedly improved and complained only of pains in his right testicle which subsequently subsided with analgesics tetracycline and local heat The temperature was elevated for two days but came down with improvement of the epididymitis On the second hospital day while being weighed he developed sudden severe substernal chest pain with shortness of breath diaphoresis and transient hypotension Physical examination was unrevealing and the ECG s remained unchanged He responded readily to oxygen and morphine He was then kept at complete bed rest and heparin prednisone and quinidine were continued He then stabilized Dermatology consultants diagnosed fungal infections of the skin and nails by potassium hydroxide smears Therapy with Tinactin was followed by marked improvement Meanwhile renal function was slightly deteriorating with creatinine of 3 and BUN of 80 mg per 100 ml The proteinuria however at most was 2 5 mg per 24 hours

On the seventh hospital day episodes of minor chest pain again occurred with shortness of breath Serial ECG s showed persistent elevation of S T segments suggestive of an active myocardial and/or pericardial process On the tenth hospital day more severe chest pain occurred with shortness of breath sweating bradycardia and hypotension the patient was transferred to the coronary surveillance unit with a diagnosis of acute myocardial infarction al

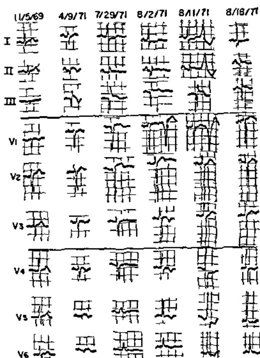


Fig 1 ECGs taken on Nov 5 1969 April 9 July 29 Aug 11 and Aug 18 1971 (see text)



Fig 2 Phlebogram of Aug 18 1969 showing occlusion of left femoral vein and of inferior vena cava at the level of the fourth lumbar vertebra There are small thrombi in the right femoral vein and extensive collateral veins



Fig 3 Phlebogram of Nov 5 1969 The thrombi in the right femoral vein are no longer present The status of the left femoral vein and of the inferior vena cava is essentially unchanged

The chest film at the time of the first admission showed the heart size to be normal The first phlebogram on Aug 18 1969 (Fig 2) showed almost complete occlusion by a large thrombus in the left femoral vein and this is seen to extend upward into the vena cava with occlusion of the vena cava at the level of the fourth lumbar vertebra There is extensive collateralization of the veins in the perivertebral plexus There are small clots in the right femoral vein The examination was repeated about three months later on Nov 5 1969 (Fig 3) It is evident that the clots in the right femoral vein have disappeared but there is essentially no difference in the left femoral vein thrombus There continue to be extensive venous collaterals Chest films showed that the patient went on to develop cardiac enlargement and intrapulmonary effusion both of which improved in response to treatment prior to the patient s death

DR SIMON Were there signs of occlusion of the renal veins?

DR LEVIN I cannot tell whether or not the renal veins are thrombosed The contrast medium did not reach the height of the renal veins so I cannot tell whether there is washout by the blood coming from the renal veins to the vena cava nor was there any attempt to catheterize the renal

number of red blood cells was noted in the urine, a finding unusual in patients with membranous glomerular disease and perhaps related to anticoagulant therapy A repeat renal biopsy was performed at this time and revealed changes suggestive of active glomerulonephritis A transition of one type of renal lesion into another is very unusual in patients with SLE in terms of both our own experience[1] and that of others[2,3]

Two years later the patient presented with another major catastrophe an acute myocardial infarction, at the remarkably young age of 21 years A Type II hyperlipoproteinemia and persistent abnormalities of the nephrotic syndrome were found, but there were no immunologic signs of active disease How can we explain the occurrence of acute myocardial infarction in this patient? SLE may produce a vasculitis involving the coronary arteries However large coronary artery occlusion with frank myocardial infarction is distinctly unusual[5,6] The patient had hypercholesterolemia and Type II hyperlipoproteinemia Serum lipid abnormalities are associated with the nephrotic syndrome regardless of etiology[7] Levels of cholesterol and triglyceride are increased due to enhanced hepatic synthesis of these lipids and retarded catabolism Types II and IV lipoprotein abnormalities are most commonly found There is an increased risk of atherosclerotic occlusive events in patients with the nephrotic syndrome Of 36 patients with membranous glomerulonephritis at our own institution four developed fatal myocardial infarction at a relatively young age[8] Berlyne and Mallick[9] estimated that the risk of fatal infarction was increased 85 times in nephrotic patients

Now we come to the last admission He re entered the hospital in July 1971 with symptoms of congestive heart failure and testicular pain Physical findings revealed a skin rash, more likely due to a superficial mycosis than to SLE, signs of congestive failure with an S_3 and S_4 gallop and epididymitis May we review the ECG s and x rays at this time?

DR H COHEN The first available ECG on this patient was on Nov 5 1969 (Fig 1) It is within normal limits On April 9, 1971, slurred Q waves have developed in Leads II, III, and V_6 The QRS complex is now mainly inverted in Leads I and V_6 and biphasic in aV_L S T segments are elevated in Leads II, III and V_3 through V_6 and T waves are inverted in these leads These changes are compatible with an acute posteroapical myocardial infarction probably with some loss of lateral myocardium as well, accounting for the slight right axis deviation Almost four months later, on July 29, 1971, QRS complexes have become widened and slurred, especially in Leads I V_5, and V_6 Q waves are no longer seen in Leads II, V_5, and V_6 The T waves are no longer inverted but S T segments remain elevated in Leads II, III, and the midprecordial leads Thus an incomplete left bundle branch block has obscured part of the features of the myocardial infarction In addition S T segment deviation has occurred partly because of the left bundle branch block, and partly because of digitalis effects, which may elevate S T segments in right precordial leads as well as in leads reflecting myocardial infarction such as Leads II and III in this case Left bundle branch block disappears by the time of the next tracing (Aug 2 1971) and Q waves are again clearly seen in Lead II so that the inferior myocardial infarction is more obvious In addition T waves have become inverted in the midprecordial leads This suggests an active process in the anterior myocardium This process may or may not be ischemic in nature Also ectopic ventricular beats have developed The last two tracings on Aug 11 and 18 1971 show a stable pattern of inferior myocardial infarction digitalis effects the development of left ventricular hypertrophy and waxing and waning of anterior ischemia like alterations I feel that the deviation of the S T segments is still on the basis of digitalis effects and left ventricular hypertrophy if there is a pericarditis here I am unable to recognize it as such mainly because of absence of the expected evolution and presence of other causes for the contour alterations

DR SOMMERS Thank you Dr Cohen

DR B LEVIN First films of bony structure demonstrate what is noted in the protocol that is the steroid effects on the bones demineralization and compression of the dorsal and lumbar vertebral bodies



Fig. 4 First renal biopsy (April 1965) Representative glomerulus showing diffuse membranous changes but no hypercellularity Small interstitial infiltrates of round cells were also present (*Hematoxylin and eosin* ×490)

suggest this possibility for several reasons The description of the initial examination during his admission in July indicates that the heart tones were of good quality and no murmurs were heard On the last admission he was admitted for congestive heart failure which was managed easily with the usual *regimen of diuretics digitalis* and salt restriction since he improved greatly within one day On the second hospital day however he developed severe substernal chest pain with associated shortness of breath diaphoresis and transient hypotension The situation seemed to have been uncertain enough so that he was admitted to our coronary surveillance unit with the presumptive diagnosis of a possible acute myocardial infarction He then developed a pericardial friction rub which *certainly* could be due to lupus pericarditis but is very commonly seen about a week after myocardial infarction in patients with myocardial *infarction* on an atherosclerotic basis alone In addition his heart tones now were noted to be muffled whereas as I pointed out before on admission they were well heard Furthermore he developed a holosystolic murmur that was not present on admission Under these circumstances we usually ascribe the holosystolic murmur that results from infarc*tion or ischemic injury* to either papillary muscle dysfunction or the development of a ventricular septal defect The patient was discharged three weeks after this possible myocardial infarction We do not know the level of his activity after discharge but the two to three week period after myocardial infarction if you will grant the possibility of an acute myocardial infarction is the time when we see myocardial ruptures or development of further infarction with arrhythmias and sudden death So although I think your diagnosis is very well taken I would consider strongly the possibility of coronary atherosclerosis

DR KANTER The protocol was somewhat unfair in that it failed to state that the patient had persistent angina pectoris be*tween the second and final hospitalizations* He may not have reported this to the house staff He was a very frightened young man who knew he was going to die The diagnosis of his initial myocardial infarction was not easy It was the fact that patients with long standing nephrotic syndrome are predisposed to arteriosclerotic disease and myocardial infarction which influenced our admitting diagnosis He presented with none of the classical features of infarction having developed *abdominal distress* during a fight with his mother and girl friend

veins Of interest, though, is that on first study I neglected to point out that we do see the calyceal system of both kidneys and they look intact The kidneys however are somewhat enlarged, measuring 15 cm in length One can see here the calyceal system on the left side and on the right side They appear grossly normal except that the kidneys are large

DR SIMON Laboratory studies initially suggested inactive disease, but immunologic parameters of activity later became abnormal The hospital course was characterized by recurrent episodes of shortness of breath chest pain, transient hypotension the appearance of a pericardial friction rub, and deterioration of renal function, suggesting a relentless downhill course However his condition improved after treatment with digitalis, diuretics and heparin to the point where he was able to leave the hospital only to die suddenly two days later

It appears that we must focus on the nature of the cardiac involvement in this patient with SLE In view of the history of previous myocardial infarction coronary atherosclerosis comes to mind first But in spite of the stormy course in the hospital serial ECG s and serum enzyme studies failed to establish the occurrence of fresh infarction Therefore I doubt that coronary atherosclerosis could account for the sequence of events during the last hospital admission

Pulmonary embolism is of course possible and was a source of serious concern to his physicians especially in view of the history of thrombosis of the inferior vena cava and leg veins Although it would be difficult to exclude pulmonary embolism significant findings are not compatible with this diagnosis—the pericardial friction rub and negative lung scan In one report on pulmonary embolism positive lung scans were obtained in all patients[10]

Finally, we may consider direct involvement of the heart by SLE There may be endocarditis affecting the valve leaflets papillary muscles and mural endocardium initially described by Libman and Sacks[11] Although endocarditis may produce systolic and diastolic murmurs it rarely is of sufficient hemodynamic consequence to result in congestive heart failure In addition endocarditis was not found in patients treated with corticosteroids[5]

Myocardial damage may occur in SLE[3,4] This is due to vasculitis of the small coronary arteries rather than to primary involvement of myocardial fibers However clinical evidence of frank myocardial infarction is unusual The findings and course in the patient under discussion are entirely compatible with active lupus myocarditis

Pericarditis is the most common manifestation of cardiac involvement in SLE[3,4] although not always evident clinically The patient presented today did have a pericardial friction rub Other alterations which contribute to cardiomegaly and congestive heart failure in patients with SLE are systemic hypertension, pulmonary hypertension from parenchymal or small vessel involvement in the pulmonary tree anemia, and fever

Therefore, I would conclude that the patient had systemic lupus erythematosus active primarily involving the heart and the kidneys The cardiac involvement was in the form of pericarditis and myocardial damage due to coronary vasculitis superimposed on atherosclerosis of the coronary arteries Examination of the kidneys will show membranous glomerulonephropathy with an unusual transition to an active glomerulonephritis As to the immediate cause of death one can only speculate since the patient was not under observation that the mechanism was an arrhythmia or pulmonary embolism

DR SOMMERS Dr Simon that was the most lucid discussion that we have heard in many a year I wonder if any of the people involved in the care of this patient before his demise would care to make a comment

DR A KANTER I enjoyed your discussion very much Dr Simon I would like to know if you have any thoughts as to what we might have done during that last admission to determine the etiology of his cardiac disease

DR SIMON I will answer that after the pathologic report

DR G GLICK I also enjoyed very much your discussion Dr Simon Just on the basis of this protocol I would think that coronary atherosclerosis may be the primary reason for the patient s death I

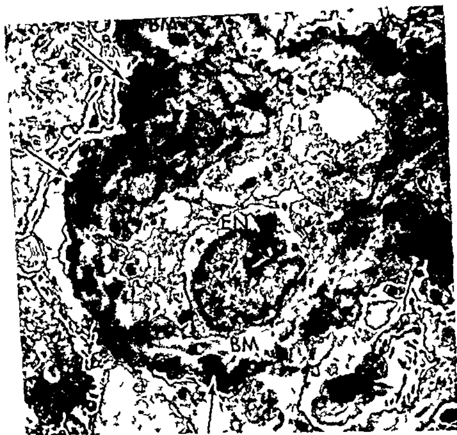


Fig 7 Second renal biopsy Electron micrograph of a glomerular capillary There were extensive electron-dense subepithelial deposits (arrows) Smaller deposits were also present within the basement membrane proper (BM) and in the mesangial areas (M) The capillary lumen (L) is narrowed by the swollen endothelial cells (EN) (X8 400)

First I will present the findings of the two renal biopsies One was obtained in 1965 at the University of Illinois It was an adequate biopsy and all glomeruli showed essentially the same changes namely a diffuse thickening of the capillary wall with normal cellularity and patent capillary lumens (Fig 4) In periodic acid-Schiff and better in silver methenamine preparations a true thickening of the basement membrane and some irregularity of its contour could be seen (Fig 5) There was a *mild* increase of mesangial matrix but this was not thought to be significant Under oil immersion it was possible to recognize projections or spikes from the *outer aspect of the* basement membrane In trichrome preparations under oil immersion the basement *membrane* and its projection from the outer aspect were blue Separating the pikes were fuchsinophilic red areas corresponding to immune deposits In brief the histologic pattern of the first biopsy was quite consistent with either that of idiopathic membranous glomerulopathy or that of the membranous form of lupus nephritis[2,13]

The second renal biopsy was obtained about four years later The disease appeared to be more active The glomerular changes were similar to those of the first biopsy except for an occasional small epithelial crescent (Fig 6) There was now an interstitial infiltrate of inflammatory cells for the most part *lymphocytes and* plasma cells which should be interpreted as a sign of activity of lupus nephritis There was more interstitial edema and fibrosis as well and in the glomerular capillaries few trapped leukocytes could be seen We must keep in mind that at this time the patient had also a reasonably



Fig 5 First renal biopsy The glomerular capillary basement membrane is diffusely thickened and its outer contour is irregular (Silver methenamine ×1 235)

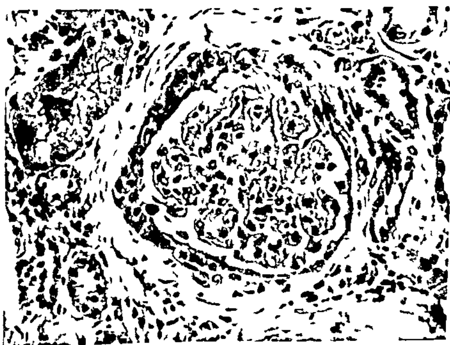


Fig 6 Second renal biopsy (November 1969) All glomeruli showed membranous changes as in the first biopsy but in addition some of them presented small epithelial crescents as shown in this figure There was also some interstitial edema and tubular atrophy (Hematoxylin and eosin ×490)

He was admitted to the hospital despite the protestations of the house staff who attributed his complaints to anxiety following a family argument Of course the ECG settled the matter

DR C I PIRANI This case was selected for a CPC first because of its long and interesting history and second because all the major clinical manifestations of this patient's illness were satisfactorily explained by the postmortem examination Dr Simon has given us a very lucid presentation nicely correlated with possible pathologic findings and this will make my task much easier

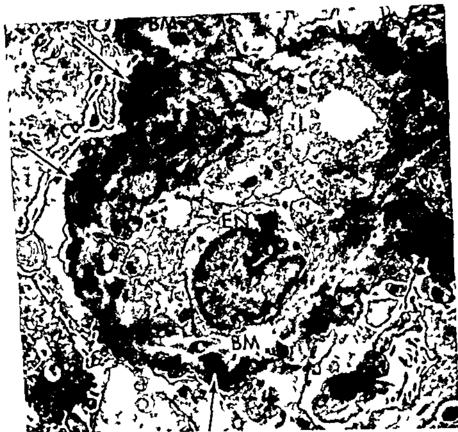


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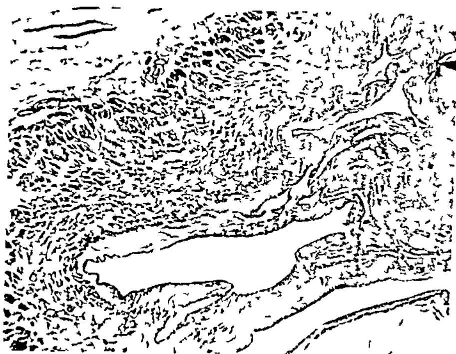


Fig 8 Cross section through the right renal vein near the inferior vena cava A well organized and recanalized thrombus is present (Hematoxylin and eosin ×40)

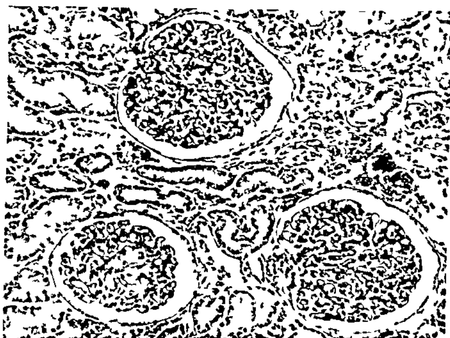


Fig 9 At autopsy moderate membranous changes were present in all glomeruli No changes of note were seen either in the tubules or in the interstitium (Hematoxylin and eosin ×200)

well documented episode of renal vein thrombosis which may have been responsible for the prominent interstitial edema [14] Electron microscopy of the second biopsy revealed the capillaries of all glomeruli studied to have a very thick basement membrane with electron dense deposits primarily in a subepithelial position but also within the basement membrane proper Electron dense deposits were also seen in the mesangial areas [15] The visceral epithelial cells showed villous transformation and the foot processes were generally fused (Fig 7) The endothelial cells were often swollen and occasionally were found to contain viruslike inclusions in their cyto

plasm—a common finding in SLE[16] In brief the electron microscopic studies confirmed the diagnosis of lupus nephritis membranous type

At the time of autopsy the external examination revealed a maculopapular skin lesion which histologically was found to be due to a mycotic infection probably trichophytosis and which we thought to be related to the low immunologic resistance of this patient There was a moderate amount of aortic atherosclerosis especially in the abdominal segment The inferior vena cava below the renal veins presented an irregular intimal surface due to a web of fibrous tissue The right renal vein also contained some bands of fibrous tissue However the lumen of both these vessels was adequately patent Histologically these bands were obviously part of a recanalized thrombus (Fig 8) The kidneys were large and had a smooth surface Histologically the renal changes were quite similar to those observed on the second renal biopsy except that all evidence of active disease was no longer present Actually the tubules were well preserved and there was little interstitial edema or fibrosis (Fig 9) There was however a mild to moderate degree of nephrocalcinosis in the renal medulla This almost certainly was related to corticosteroid therapy as was the extremely severe osteoporosis seen in sections from the vertebrae confirming the x ray findings As we have occasionally seen in patients with osteoporosis even with normal serum calcium levels there was a mild degree of parathyroid hyperplasia However no changes of osteitis fibrosa or of increased osteoclastic activity were seen The spleen showed atrophic lymphoid tissue and the adrenal cortices were somewhat reduced in size both changes obviously secondary to corticosteroid therapy The heart weighed 470 grams much of this increased weight due to the abundant subepicardial fat Thus hypertrophy was considered to be only mild to moderate On cross section the right coronary artery a few centimeters from its orifice was seen to be occluded by a recent thrombus Histologically the thrombus could be seen to have formed over an atheromatous plaque (Fig 10) The left circumflex coronary artery was completely occluded by an old athero



Fig 10 Cross section through the right coronary artery showing extensive atheromatous changes and a superimposed recent thrombus (Hematoxylin and eosin ×65)

sclerotic process with calcification Other coronary arteries presented considerable atherosclerosis There was a rather large infarct in part old and in part recent involving primarily the posterior aspects of the interventricular septum and of the left ventricular wall The left papillary muscles all the way to their apex were involved by fibrosis and by very recent ischemic necrosis probably no more than two days old (Fig 11) This lesion was almost certainly responsible for the holosystolic murmur heard a few days before death A small organizing mural thrombus was attached to the area of infarction in the left posterior wall which was estimated to be six to eight weeks old To complicate matters in the periadrenal adipose tissue a few small arteries presented the classic changes of acute arteritis a possibility that Dr Simon mentioned The inflammatory cells consisting of polymorphonuclear leukocytes lymphocytes and plasma cells extended through the entire thickness of the wall in which fibrinoid changes were also present (Fig 12) No microorganisms were seen with the use of special stains The possi

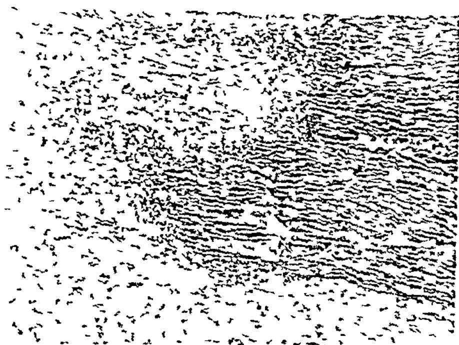


Fig 11 Section through a left papillary muscle showing recent myocardial necrosis (right) and an organizing infarct (left) (Hematoxylin and eosin ×52)



Fig 12 Periadrenal arteriole with acute inflammatory changes involving its wall (Hematoxylin and eosin ×220)

bility of hypersensitivity was considered but no eosinophils were present in the inflammatory infiltrates and no arteritic lesions were seen in any other tissue Death was attributed to heart failure as evidenced by the severe edema and congestion of the lungs So most if not all of the symptomatology of this patient can be satisfactorily explained by the autopsy findings

This patient for 19 years or more had a form of lupus nephritis which has a very good prognosis indeed not dissimilar from that of idiopathic membranous glomerulonephropathy These patients can live a long life as long as the other symptomatology and complications of SLE can be controlled It is of interest that the episode of renal vein thrombosis appeared to have

ggravated the renal disease only tempo arily This may have been due to the prompt diagnosis and treatment of this complication As a result of the nephrotic syndrome and persistent hyperlipidemia severe atherosclerosis particularly of the coronary arteries developed early in the life of this patient and led to the occlusion of two major coronary arteries and exten sive myocardial infarction The possibility that periarteritis may have facilitated the development of atherosclerosis does not seem likely The isolated periadrenal ar teritis remains unexplained but there was no evidence of either old or recent arteritis in the coronary arteries

DR SIMON I steered away from the diag nosis of coronary atherosclerosis as the primary cardiac lesion because of the find ing of a pericardial friction rub and the absence of confirmatory evidence of myo cardial infarction This line of thinking was based on the assumption that the presence of a pericardial friction rub in a patient with myocardial infarction would indicate a transmural infarct which should be re flected in diagnostic ECG and serum en zyme changes It is sobering to realize that our constrictive ways of thinking are not always valid and that Dr Glick s summation was more accurate than my own

An important issue raised by this case is the need to alter our approach to the pa tient with the nephrotic syndrome in that attention must be paid not only to the kidneys but also to the significant lipid and coagulation abnormalities that are present with the enhanced risk of athero genesis and thrombotic events If treatment of the underlying renal lesion produces a remission of proteinuria we may expect resolution of the associated lipid and clot ting abnormalities However if treatment is unsuccessful in altering proteinuria then direct therapeutic efforts at lowering serum lipids by diet and drugs and preventing thrombosis through the use of anticoagu lants should be strongly considered

In a recent report arteritis of a large coronary artery with occlusion and myo cardial infarction was demonstrated in a 16 year-old girl with SLE[12] In addition angiographic abnormalities of major coro nary vessels were found in three other young women All had angina pectoris and two sustained myocardial infarctions

DR S KABINS I just want to ask Dr Glick whether somewhere in the last month or so before he died this patient might have been a candidate for coronary angiography or coronary bypass surgery?

DR GLICK The answer to both questions is yes I would have considered him a candi date for both angiography and surgery However I have great doubt that either of these procedures would have been car ried out We do coronary angiography only when we think corrective surgery is in the cards and in view of his primary disease I doubt that we would have thought that surgery would have been helpful

DR SOMMERS Any more comments or questions from the audience? If not thank you very much

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Table I Classification of cases of CAVO without splenic abnormalities and their relationship to Down's syndrome

Complete					Various complexes of CAVO	Incomplete				
N†	D†	U†	T†	Total		Total	N	D	U	T
					A In levocardia (normal position of the heart) with situs solitus organs					
					1 Simple (without other complexes)					
15	30	2	0	47	a Balanced	11	9	2	0	0
2	1	0	0	3	b Dominant right	3	3	0	0	0
3	1	0	1	5	c Dominant left	1	1	0	0	0
				55		15				
					2 Complicated (associated with other complexes)					
7	7	0	0	14	a Fetal coarctation	10*	10	0	0	0
0	8	0	0	8	b Patent ductus arteriosus	1	0	1	0	0
1	0	0	1	2	c Pulmonary stenosis					
4	10	1	0	15	d Tetralogy of Fallot	1	0	1	0	0
7	0	1	0	8	e Double outlet right ventricle	1	1	0	0	0
3	0	1	0	4	f Complete transposition					
9	3	1	0	13	g Absence of atrial septum					
0	1	0	0	1	h Absence of posterior ventricular septum					
					i Aortic stenosis	1	1	0	0	0
4	0	0	0	4 (partial)	j Total or partial anomalous pulmonary venous drainage	1 (total)	0	1	0	0
2	0	5	0	7	k Single ventricle					
1	0	0	0	1	B In mixed dextrocardia (atria pivotal ventricles in mirror image)					
2	0	0	0	2	C In isolated levocardia with atrial situs inversus					
2	0	0	0	2	D In isolated levocardia with atrial undeterminate with situs inversus organs					
1	0	0	0	1	L In mesocardia with atrial situs solitus and ventricles in mesoversion					
0	1	0	0	1	I In mesocardia—indeterminate type					
				83		15				

*Includes 2 cases of adult coarctation
†Abbreviations D = Down's syndrome N = Down's syndrome absent T = Trisomy 18 U = Unknown whether Down's syndrome present or not

dominant left form (Fig 2), the left ventricle is markedly hypertrophied and enlarged, but the right ventricle is smaller than normal, with a normal or thickened wall These three forms were found in both types complete and incomplete and most complexes of CAVO In the incomplete type in the complexes with fetal coarctation, and in all types of dextrocardia, there was a greater tendency for the occurrence of the right ventricular form than in the other complexes

The term *mixed dextrocardia* (in Tables I, II, and III) implies that the base apex of the heart points to the right and caudal ward and the atria and ventricles do not correspond The term *presumptive* in Mirror image dextrocardia (Table II) implies that the atrial septum is absent or inconclusive in its morphology as to its right or left side and hence only a presumptive diagnosis is made of the atria from the atrial appendages

In consideration of abnormalities of the spleen all abnormalities were included in this study both minor and major Even though accessory spleens and occasionally abnormal lobulation of the spleen may occur in the normal person yet they may conceivably represent a forme fruste of asplenia and polysplenia, and hence they are included in this study

Table 11 Classification of cases of CAVO with splenic abnormalities and their relationship to Down s syndrome

Complete											Various complexes of CAVO	Incomplete										
N†	D†	U†	T†	A†	P†	AC†	B T M†	H†	MA†	Total		Total	N	D	U	T	A	P	AC	B T M	H	MA
											A In levocardia with situs solitus organs											
											1 Simple											
1	1	0	0	0	0	1	1	0	0	2	Balanced											
											2 Complicated											
0	2	0	0	0	0	2	0	0	0	2	a Fetal coarctation	2	1	1	0	0	0	0	1	1	0	0
0	1	0	0	0	0	1	0	0	0	1	b Patent ductus arteriosus	1	0	1	0	0	0	0	1	0	0	0
1	0	0	0	1	0	0	0	0	0	1	c Pulmonary steno is											
6	0	2	0	6	0	1	0	1	0	8	d Double outlet right ventricle											
2	0	1	0	2	0	1	0	0	0	3	e Complete transpo ition											
0	0	0	2	0	0	1	0	0	1	2	f Aortic atresia and interrupted aortic arch											
3	0	2	0	4	0	0	1	0	0	5	g Single ventricle											
0	0	1	0	0	0	1	0	0	0	1	h Truncus											
											B In dextrocardia											
6	0	0	0	4	1	0	1	0	0	6	1 Presumptive mirror image type											
1	0	0	0	1	0	0	0	0	0	1	2 Mixed dextrocardia (atria pivotal ventricles in mirror image)											
5	0	0	0	4	0	0	1	0	0	5	3 Type undetermined	1	1	0	0	0	0	1	0	0	0	0
											C In i olated levocardia											
4	0	0	0	4	0	0	0	0	0	4	1 With solitus atria											
17	0	0	0	10	2	4	1	0	0	17	2 With indeterminate atria	3	3	0	0	0	0	2	1	0	0	0
											D In me ocardia											
1	0	0	0	0	1	0	0	0	0	1	1 Presumptive mesoversion with atrial situs solitus and ventricles in mesoversion											
1	0	0	0	0	0	1	0	0	0	1	2 Mixed me ocardia with atrial situs solitus and ventricles inverted											
1	0	0	0	0	0	1	0	0	0	1	3 Indeterminate type											
										61		7										

Incl de t ase of adult coa ct ti
†Abbre i tl A = A ple i AC = Accessory pl n B T M = Bil bed tril bed o multilobed spleen D = Down s sy d ome H = Hypopla ia of spleen MA = Malformation of pleen N = Down s y d m abse t P = P ly pl ia T = T isomy 18 U = Unknown wheth Do s synd me p se t or n t

Table III. Classification of cases of CAVO in which the status of the spleen is unknown and their relationship to Down's syndrome*

Complete					Various complexes of CAVO	Incomplete				
N†	D†	U†	T†	Total		Total	N	D	U	T
					A. In levocardia with situs solitus organs					
					1. Simple					
3	3	7	0	13	a. Balanced	6	5	0	1	0
					b. Dominant right					
0	1	0	0	1	c. Dominant left					
					2. Complicated					
0	1	0	0	1	a. Fetal coarctation	1	1	0	0	0
1	2	0	0	3	b. Patent ductus arteriosus					
1	0	0	0	1	c. Pulmonary stenosis					
1	0	2	0	3	d. Tetralogy of Fallot					
0	0	1	0	1	e. Double outlet right ventricle					
0	0	1	0	1	f. Complete transposition					
2	0	1	0	3	g. Absent atrial septum					
0	0	1	0	1	h. Total anomalous pulmonary venous drainage					
0	0	1	0	1	i. Truncus					
1	0	2	0	3	j. Single ventricle					
					B. In dextrocardia					
0	0	2	0	2	Mixed dextrocardia with atria situs solitus and ventricles inverted					
				34		7				

*In this group the status of the spleen could not be ascertained because (1) only a chest autopsy was done, or (2) the autopsy protocol did not distinctly indicate what the status of the spleen was, or (3) the autopsy protocol was not available.

†Abbreviations: D = Down's syndrome; N = Down's syndrome absent; T = Trisomy 18; U = Unknown whether Down's syndrome present or not.

*Table IV. Occurrence of Down's syndrome in the various complexes of CAVO**

Type	Occurrence
Complete simple without splenic abnormalities	60.4%
Complete complicated without splenic abnormalities	40.5%
Complete with splenic abnormalities	7.3%
Incomplete simple without splenic abnormalities	13.3%
Incomplete complicated without splenic abnormalities	20.0%
Incomplete with splenic abnormalities	28.6%
Complete with positional abnormalities of the heart and organs with normal spleen	14.3%
Complete and incomplete with positional and splenic abnormalities	0.0%

*Percentages do not indicate incidence of the anomalies in Down's syndrome.

The ductus arteriosus is mentioned as being patent only if it is so after 3 months of age. Below 3 months of age it is considered to be normal.

The AV valve in CAVO

The three types of anterior bridging leaflets seen in the complete form described by Rastelli and colleagues[28, 35, 43] were also found in our material. In their first type there are attachments of the anterior bridging leaflet by chordae to both sides of the ventricular septum. In their second type the anterior bridging leaflet was unattached to the septum but attached medially to an anomalous papillary muscle in

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Fig 1 *A* and *B* Dominant right form of CAVO intermediate type *A* Right atrial and right ventricular view *B* Left atrial and left ventricular view *RA* = right atrium *RV* = right ventricle *LA* = left atrium *LV* = left ventricle



Fig 2 *A* and *B* Dominant left form of CAVO complete type *A* Left atrial and left ventricular view *B* Right ventricular view *LA* = left atrium *LV* = left ventricle *A* = aorta *RV* = right ventricle *PA* = pulmonary trunk

the right ventricle In their third type the anterior bridging leaflet was a free floater being unattached to the septum above but attached to the usual papillary muscles on both sides The first and third types of these authors however are not sharply demarcated as categories in our material Some free floating leaflets were completely free floating with connections of the leaflet only to the left anterior and right antero lateral papillary muscles with no muscle of Lancisi being present Others had a few chordal attachments to the summit of the ventricular septum either on the right or left side Still others had wide attachments of chordae to both sides of the summit The annulus of this leaflet likewise had a varying morphology It was usually attached to the non coronary and to the adjacent part of the left coronary cusp by way of the *pars membranacea* and what may be called the aortico mitral annulus The

connection in some cases involved also the posterior extremity of the *right aortic cusp* and in a rare case extended throughout the whole base of the right aortic cusp with a varying amount of attachment on the summit of the anterior basal portion of the *ventricular septum*. The morphology of the posterior bridging and lateral leaflets was as described by Rastelli and co workers[8,35,43]

The right anterolateral papillary muscle was usually widely attached to the wall often had multiple components, and in some cases was prolonged extending into the annulus of the anterior bridging leaflet. The right inferior papillary muscle in some cases was absent while in others there were several such structures. The left anterior and posterior papillary muscles were in some cases situated more laterally than normal. These muscles were in some instances small and occasionally they proceeded to the base of the valve rather than to the edge. Only an occasional case of the second type of Rastelli and co workers[28,35,43] was seen with a small papillary muscle attachment to the right side of the septum. Two cases of double orifices were seen on the mitral side and 3 cases of double orifices on the tricuspid side.

In the incomplete (intermediate transitional) type as described by Wakai and Edwards[6] valvular tissue was seen on the summit of the ventricular septum. In some cases this was an extension of the posterior bridging leaflet. In others it appeared to be an independent component.

Alterations in the annular relationships of the anterior bridging leaflet were found in CAVO associated with tetralogy of Fallot double outlet right ventricle and in complete transposition. In tetralogy of Fallot the anterior bridging leaflet was almost always a "free floater". In some of these cases the base of the leaflet was related more to the left than to the noncoronary cusp. The right anterolateral papillary muscle was usually abnormally large, widely based, and its chordae often formed a sheet containing muscle extending to the base of the valve. In double outlet right ventricle and in partial transposition with pulmonary atresia (*pseudotruncus*) the anterior bridging leaflet was always a "free floater". Its annulus was either related to the aorta by way of the *pars membranacea* or to an extention of the central fibrous body, or it was separated from both the aorta and the pulmonary trunk by conal musculature. In complete transposition there was almost always pulmonary atresia and the base of the anterior bridging leaflet in almost all cases was separated from the aorta by conal musculature. In complicated types in general there was a strong tendency for the anterior bridging leaflet to be a "free floater."

Alterations of the attachments of the common AV valve to the papillary muscles were found in single ventricle. Here there was usually a group of anterior and posterior papillary muscles with a varying number of leaflets.

The attachment of the leaflets in the dominant right and left forms deserves attention. In the latter in many cases the only attachment in the right ventricle was that of the anterior bridging leaflet to the anterolateral papillary muscle while the remainder of the valve was attached to the left ventricle. In the dominant right type, the attachment of the leaflets were as in the balanced form but the left portions were small and the right large.

Discussion

In our material without splenic abnormality CAVO both complete and incomplete types occurs as a complex by itself or associated with other complexes among which most common are fetal coarctation patent ductus arteriosus tetralogy of Fallot double outlet right ventricle absence of the atrial septum and single ventricle. Less commonly it is associated with pulmonary stenosis absence of the posterior part of the ventricular septum complete transposition aortic stenosis or atresia interruption of the aortic arch and truncus communis. It may be noted that despite a normal spleen it occasionally is associated with dextrocardia isolated levocardia and mesocardia. It is also of interest that in our material without splenic abnormalities, there are more cases of the complete complicated type than the complete simple type. If this should prove to be true for other series this needs to be kept in mind in the efficacy of surgical treatment.

In all types complete and incomplete simple or complicated with or without

a plenia there may be dominant right and dominant left forms We have chosen to delineate the dominant right and dominant left forms of CAVO as those in which the smaller of the two ventricles is smaller than normal rather than those in which one chamber is larger than the other We believe this is justified from the surgical ta id point As long as a chamber is normal in size and thickness it is presumed that at least theoretically a case of CAVO may be operable When however a chamber is smaller than normal there is some question as to the operability of the case

The question of the tendency towards dominance of the right or the left sides in some cases of CAVO has not been explained In favor of an embryological explanation for the dominant left form are the tenuous attachments of the valve to the right ventricle reminiscent of a primitive ventricle perhaps of the same type as found in the anomaly straddling tricuspid orifice [50] However *there may be physiologic reasons* for dominance of either side which have not yet come to the fore in correlative catheterization and anatomic studies

The association of CAVO with splenic abnormalities is well known [1 53] Our material shows that this may occur with normal or abnormal situs of organs Where there is situs solitus in the complete type only rarely is the association found in the simple type or with fetal (preductal) coarctation and patent ductus arteriosus when the association is present there is usually only an accessory spleen or abnormal lobation of the spleen However when the complete form in situs solitus is complicated by pulmonary stenosis double outlet right ventricle aortic atresia absence of the atrial septum or single ventricle the association *with splenic abnormalities* is frequent and there usually is asplenia Hence in situs solitus the simple type of CAVO *does not* show severe abnormalities of the spleen but the complicated form may *show such* abnormality The incomplete type simple or complicated in situs solitus is *rarely* associated with splenic abnormalities and then only with an accessory or multilobed spleen Where there is abnormal situs of organs as is well known [53 54] the association of CAVO with asplenia or polysplenia is strong

As concerns the relationship of CAVO to Down s syndrome as is well known the complete simple type without splenic abnormalities shows a frequent association As compared with the complete simple type this association *is less marked in the complicated type* ($p < .05$) As compared to the complete simple form there is a less frequent association of the incomplete type without splenic abnormalities with Down s syndrome ($p < .01$) Interesting is the relative lack of association of *the complete* type with Down s syndrome where there are abnormalities of the spleen as compared to CAVO without the latter ($P < .001$) The reason for this inverse relationship is unknown to us

From the standpoint of longevity as gleaned from autopsy statistics the incomplete simple type has a greater longevity than the complete simple type Fetal coarctation in CAVO is relatively lethal in both complete and incomplete types whereas *the presence of a* ductus arteriosus in the complete simple type may be beneficial Splenic abnormalities in CAVO are associated with less viability than those cases with normal spleens

Summary

A study was made of the incidence of CAVO as it occurs by itself *and as it is* associated with other complexes and the association of these complexes with Down s syndrome and splenic abnormalities It was found that the complete complicated type (associated with other abnormalities) is more common than *the complete* simple type where there are no *splenic abnormalities* All types complete and incomplete had balanced dominant right and dominant *left forms* which is important surgically *The simple type* in situs solitus does not show severe abnormalities of the spleen but the complicated type does Incomplete types are rarely associated with severe abnormalities of the spleen

The *complete* complicated type without splenic abnormalities is less often associated with Down s syndrome than is the complete simple and the incomplete less often than the complete type There is an inverse relationship between Down s syndrome and CAVO associated with splenic abnormalities

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In all types complete and incomplete simple or complicated with or without

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The association of patent ductus arteriosus with CAVO is favorable, and the association with fetal coarctation or splenic abnormalities is unfavorable for longevity

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Case report

P. S., a 5½ year old boy from Italy, was well until six months before admission when his mother noted that his heart was beating rapidly. He was asymptomatic except for pallor when examined at that time, but his heart rate was found to be 240 and later 180 beats per minute on two separate examinations. Treatment with diazepam was started but had no effect. He was hospitalized in Rome and treated sequentially with oral digoxin, intravenous digoxin, and oral quinidine without response. Next he received an intravenous course of methoxamine and quinidine without improvement. Since his antistreptolysin titer was noted to be 650 Todd units, the diagnosis of rheumatic carditis was considered, though there were no clear cut manifestations of rheumatic fever. He received a course of cortisone and digoxin therapy for 20 days. Following this he was treated with a combination of propranolol and digoxin and his heart rate slowed to a constant rate of 150 beats per minute. Three weeks prior to his first evaluation by us, he underwent a tonsillectomy for chronic tonsillitis. His heart rate persisted at 150 beats per minute without medication throughout this period.

The patient was first seen by us in April, 1972. He presented as a well developed, well nourished, asymptomatic boy who appeared quite comfortable. Weight 50¼ lbs, height 43 inches, pulse 152 and regular, blood pressure 110/80. His chest was symmetrical. The PMI was in the fifth left intercostal space inside the midclavicular line. There were no murmurs. The ECG showed a coronary sinus rhythm with inverted P waves in Leads 2, 3, and aVF. A 12 hour continuous tape recording of Lead 2 was obtained. This showed persistence of an ectopic atrial focus evidenced by inverted P waves. The rate was fixed at 152 beats per minute.

He was admitted for further evaluation and possible cardioversion. Serum potassium and thyroxine levels were normal. The hematocrit was 39 per cent, white blood count was 10,000, with a normal differential. At cardiac catheterization his right heart pressures were normal and there was no evidence of an intracardiac shunt. There was a thin rad opaque layer along the right atrial wall that was quite obvious during fluoroscopy. Intra atrial ECG recording showed upright P wave only when the catheter was near the tricuspid valve. Attempts to convert the rhythm to a normal sinus rhythm with intravenous procainamide 200 mg. and propranolol 0.5 mg. were unsuccessful. Bipolar atrial pacing at a rate of 600 per minute was ineffective. However, after an additional dose of 200 mg. of procainamide intravenously, bipolar overdrive atrial pacing at 600 per minute for several seconds was followed by conversion to a regular sinus rhythm with a rate of 88 beats per minute for two minutes. A third dose of procainamide (100 mg.) resulted in a return to a regular sinus rhythm for eight minutes. Thereafter the tachycardia returned and although 500 mg. of procainamide, 1 mg. of propranolol, and 6 mg. of diphenylhydantoin were given prior to another attempt at overdrive atrial pacing, the tachyarrhythmia persisted. The patient developed a regular sinus rhythm in association with the vigorous crying that was induced when the pacing catheter

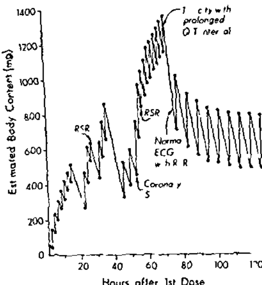


Fig. 1. Course of high dosage quinidine therapy. Ordinate represents estimated body content of drug. It was estimated by assuming 100 per cent absorption immediately upon administration and a net half life of eight hours. Regular sinus rhythm (RSR) was present when the level exceeded 450 mg. Toxicity developed when the level exceeded 1,300 mg. and resolved when it fell to 800 mg. The final regimen (300 mg. every six hours) established a plateau of concentration ranges between 500 mg. and 800 mg. This succeeded in preventing recurrence of the arrhythmia.

was removed, but his atrial tachycardia recurred after two hours of normal rhythm. It continued without change thereafter despite the administration of procainamide 1.5 Gm. and propranolol 10 mg. for one day, followed by the same dose of propranolol and first 2 Gm. and then 3 Gm. of procainamide on the two succeeding days. On the third day of this sequence he appeared pale and developed abdominal pain. The ECG continued to show ectopic atrial tachycardia with a rate of 155 beats per minute. The QRS complex, which had measured 0.06 second previously, was prolonged to 0.08 second. Procainamide therapy was discontinued.

We decided to attempt cardioversion with high doses of quinidine (Fig. 1). After a test dose of quinidine, a dose of 100 mg. was administered every two hours for eight doses without success. The dose was then increased to 200 mg. every two hours. After the second dose, regular sinus rhythm returned. The next dose was lowered to 100 mg. in order to avoid intoxication. However, the coronary sinus rhythm returned two hours later. The following day the 200 mg. every two hours regimen was resumed and sinus rhythm returned after the third dose. Since he developed mild hypotension, the quinidine was withheld for eight hours. Thereafter the regimen was changed to 200 mg. every four hours, but this led to return of the arrhythmia. The dose of quinidine was increased to 300 mg. every two hours and after the

Drug therapy of heart disease in pediatric patients III. The therapeutic challenge of supraventricular tachyarrhythmias in infants and children

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Cardiac arrhythmias in the pediatric age group are a serious problem although they occur less frequently than in adults The incidence of specific types of arrhythmias varies considerably in comparison to adults for example atrial flutter and fibrillation are less commonly encountered in children whereas paroxysmal supraventricular tachycardia may occur as frequently in both age groups

The etiology of arrhythmias in children includes congenital heart disease (e g Ebstein s anomaly frequently occurs with supraventricular tachycardias and corrected transposition of the great arteries is frequently associated with atrioventricular block) rheumatic fever infectious diseases metabolic diseases and electrolyte disturbances Arrhythmias may also be produced by tumors drugs mechanical manipulations (e g cardiac catheterization) and trauma secondary to open heart surgery In almost half of the cases however no cause can be determined

Arrhythmias in the pediatric age group may be categorized as follows (1) the persistent tachyarrhythmias where the atrial and/or ventricular rate is excessive for age (2) the persistent bradycardias where the ventricular rate is slower than normal and the cardiac output may be inadequate for proper perfusion and (3) intermittent irregularities (e g premature ventricular contractions or premature atrial contractions of less serious physiological consequence)

The only treatment for cardiac arrhythmias prior to several years ago had been the use of pharmacological agents Recently the advent of direct current cardioversion and cardiac pacing has broadened our approach to the treatment of the arrhythmias Most of the arrhythmias seen in infancy and childhood respond to pharmacotherapy but occasional refractory cases may pose a particularly challenging problem The following report details an unusually refractory case of tachyarrhythmia in a child

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Table I Antiarrhythmic drugs in pediatric practice

Drug	Type of arrhythmia					Contraindications	Dosage†
	Supraventricular tachycardia	Atrial flutter	Atrial fibrillation	Ectopic ventricular arrhythmia	Arrhythmia secondary to digitalis toxicity		
Digoxin	++	(+)	++			Supraventricular tachycardia with AV block, ventricular arrhythmia (Use with caution in AV block)	0.07 mg/Kg < 1 yr; 0.06 mg/Kg 1-2 yrs; 0.04-0.05 mg/Kg > 2 yrs — Total digitalizing dose i.m./p.o. (If i.v. total dose 75% of above)
Diphenylhydantoin	(+)			+	++	Use with caution in AV block	2-3 mg/Kg i.v.
Lidocaine	−	−	−	++	(+)	Hypotension	1 mg/Kg i.v.
Propranolol	++	+	++	(+)	(+)	Congestive heart failure, AV block, obstructive lung disease	0.05-0.1 mg/Kg i.v.; 0.5-1 mg/Kg p.o. (up to 3 mg/Kg/day)
Procainamide	(+)	(+)	+	++	(+)	AV block	3-5 mg/Kg i.v.
Quinidine	+	(+)	++	(+)	(+)	AV block	30 mg/Kg/day p.o. (Usually divided into 5 equal doses)
Potassium salt	in cases of low serum potassium concentrations						0.3-0.5 mEq/Kg/hr i.v.

Symbol: ++ = drug of choice; + = moderately effective; (+) = varying degree of effectiveness; − = not effective. †All antiarrhythmic drugs [illegible] must be given slowly. Diphenylhydantoin, lidocaine, propranolol [illegible] procainamide may be repeated [illegible] the same dosage after 20 minutes.

portant to differentiate the therapy of the simple paroxysmal tachycardia in infants and children from the management of the repetitive or persistent tachycardias. In all cases vagal stimulation should be attempted first. This can be achieved through pressure upon either the eyeballs or the area of the carotid sinus. If eyeball pressure is applied, care must be taken not to damage the structures themselves. The Valsalva maneuver may be useful in terminating the arrhythmia, but is not applicable in most young pediatric patients. The use of other physical maneuvers such as forceful slap on the chest or external cardiac massage may also be successful in some cases.

When physical methods fail, digoxin has been the drug of choice for treatment of simple paroxysmal supraventricular tachycardia in infant patients for many years. The majority of patients will eventually respond to digitalis, especially if propranolol is added as a second drug. The duration of therapy necessary may vary considerably, however. The availability of direct current countershock as a safe and reliable method[8,10] to convert the arrhythmia to a normal sinus rhythm without delay has caused us to alter the usual therapeutic recommendation for seriously ill patients.

We withhold digoxin since treatment with direct current countershock may be quite hazardous in the digitalized patient because of the possible excitation of ventricular arrhythmias. We presently attempt cardioversion in these infants first with diphenylhydantoin or propranolol (Tables I and II). Each of these drugs has been used with some success in children with this arrhythmia. The advantage of these agents is that their effect can be seen within minutes and their presence does not contraindicate the use of countershock therapy. If the serum potassium level is low, potassium is given (phenylephrine, methacholine and neostigmine are rarely used in pediatric patients). If the arrhythmia persists, we proceed to direct current countershock. It is our practice to begin with a shock of 10 Watt seconds in young infants

second dose regular sinus rhythm returned. He was maintained with 200 mg. of quinidine every two hours thereafter. He developed nausea, vomiting, and sinus tachycardia after the eighth dose and quinidine therapy was stopped temporarily.

From this experience it was obvious that it was possible to suppress the ectopic pacemaker with high levels of quinidine and that the therapeutic index (therapeutic dose/toxic dose) was small. Since it was not possible to measure serum quinidine levels, we approximated the biological half life of quinidine in this patient to guide us in calculating an appropriate therapeutic regimen.

We assumed that the half life of quinidine in this child was about eight hours. We estimated that his rhythm became normal when the amount of total body quinidine exceeded 500 mg. and that he developed toxic effects when it exceeded 900 mg. We calculated that a dose of 300 mg. every six hours would keep his total body quinidine between 500 mg. and 900 mg. He received quinidine according to this regimen for the next two days in the hospital and continued to have a normal sinus rhythm without signs of toxicity. He was discharged from the hospital and continued to be treated according to this same quinidine regimen for the next three months with persistence of regular sinus rhythm. The dose was tapered gradually over the following several months. He is presently taking 675 mg. per day and is doing well. There are no signs of quinidine toxicity. On rare occasion, especially at times of great excitement (i.e., Christmas day), the patient has experienced short episodes of the tachyarrhythmia. These have responded well to rest and none has lasted more than 30 to 40 minutes.

The etiology for the tachycardia and abnormal pacemaker in this child is obscure. Perhaps a low grade viral pericardial myocarditis might have led to both the calcification and the ectopic atrial focus which initiated the arrhythmia. Skin tests for tuberculosis and histoplasmosis were negative. There was no clinical history of an overt pulmonary or pericardial infection in the past.

This case illustrates the difficulties which may be encountered in the treatment of cardiac tachyarrhythmias and also the variety of methods available for their management.

Discussion

There are three types of supraventricular tachycardias which occur in the pediatric age group. The most frequent is the simple paroxysmal supraventricular tachycardia. It occurs most frequently in infancy, especially under four months of age. It is more common in males than in females. It is characterized by a sudden onset and termination, fixed cardiac rates in excess of 180 beats per minute, a brief duration (hours to days), and a prompt response to drug therapy. Among the patients in one large series,[1] the etiology of paroxysmal supraventricular tachycardia during infancy and childhood included Wolff-Parkinson-White syndrome (10 per cent), congenital heart disease (20 per cent), infections, injuries, heart tumors, and drugs (20 per cent), and idiopathic (50 per cent). Most cases which occur in infancy are in the idiopathic group. The presenting symptoms in infants most often include pallor, restlessness, and poor feeding. This frequently proceeds to frank congestive heart failure, and prompt treatment is mandatory. On the other hand, the older child may present with fever, chest or abdominal pain, and palpitations. In most instances the prognosis for infants with supraventricular tachycardia is good and the chance of recurrence decreases considerably after the first year of life. The prognosis for children with supraventricular tachycardia is generally related to the nature of the underlying heart disease.

The second type of supraventricular tachycardia seen among pediatric patients occurs less frequently than the "simple" type. It is referred to as "repetitive paroxysmal tachycardia."[2,3] This form consists of paroxysms of ectopic beats interrupted by short runs of sinus rhythm. This arrhythmia is resistant to therapy but is not associated with the development of congestive heart failure and therefore carries a favorable prognosis.

The third form of the arrhythmia is encountered very infrequently and is referred to as the "sustained ectopic tachycardia" or "persistent supraventricular tachycardia."[1,4,5] It is characterized by the presence of an abnormal P wave, which is always easy to discern, and by a variable rate. The rate frequently shows diurnal variation. This form of tachycardia, usually associated with an ectopic focus, may persist for many months or years despite therapy. The prognosis for the majority of children with this type of arrhythmia is good. However, two cases of cerebrovascular accidents and several cases with congestive heart failure have been reported.[1,4]

The arrhythmia in the patient reported above seemed to be of the third type. In the light of the possibility of complications occurring if the arrhythmia went uncontrolled, it was decided to attempt to convert it to regular sinus rhythm despite the fact that he had no symptoms. It is im-

Inotropic effect	*Refractory period duration*			*Toxic effects*
	Atrial myocardium	*Ventricular myocardium*	*A V node*	
− −	↓	↓	↑	AV block arrhythmias g i tract symptoms
0	↓	↓	↑	Hypotension
0	0	0	0	Hypotension convulsions
	↑	↑	↑	AV block hypotension
(+)	↑	↑	↓	AV block QRS widening hypotension
+	↑	↑	↓	QRS widening ventricular arrhythmias hypotension g i tract symptoms

+) = m ma pos t e ffe t 0 = n effe t − − = t ng n g t v effect − = mod te neg ti effect ( ) = m n m l negat e ffect.

way in which it may work is by the interruption of a fixed circus or reciprocating pathway through the atria and especially in the area of the atrioventricular junction [12] This method has been successful in converting paroxysmal supraventricular tachycardia to a normal sinus rhythm in 70 per cent of adult patients[12] and it is probable that it will have a salutory effect upon the arrhythmia in most infants and children as well

In treating a child with the sustained or ectopic form of supraventricular tachycardia it is possible that one will have to be satisfied with the control of the ventricular rate without conversion of the atrial arrhythmia It is generally considered a matter of personal preference as to which sequence of pharmacological agents is followed We prefer to start with diphenylhydantoin because it has a minimal negative inotropic effect and acts within minutes We prefer to use the beta adrenergic blocking agent propranolol as the second drug in the treatment of such patients Its antiarrhythmic mechanism is related to both its adrenergic blocking effect and its ability to depress conductivity *in a quinidine like manner* This drug should be used with caution in cases with severe congestive heart failure and is contraindicated in patients with atrioventricular block or obstructive lung disease

Procainamide may be useful in the treatment of refractory cases of supraventricular tachycardia but it is generally more effective in the treatment of ventricular arrhythmias Digoxin (or other digitalis glycosides) is the final drug on our usual list It acts by increasing the refractory period of the atrioventricular node and thereby slows the ventricular rate In some cases it acts to abolish the arrhythmia itself More often quinidine is required as an additional drug to suppress the ectopic pacemaker in these complicated cases

All of these drugs were used *in our* patient at one time or another during his hospital course However they did not alter the activity of the ectopic pacemaker Following the use of pharmacotherapy it was decided *to attempt* atrial pacing in this

*Table II. Mechanism of action and toxic effects of antiarrhythmic drugs**

Drug	Purkinje fibers action potential duration / refractory period duration	Automaticity of: Purkinje fibers	Automaticity of: Atrial myocardial fibers	Automaticity of: Ventricular myocardial fibers	Inotropic effect
Digitalis glycosides		↑	↑	↑	++
Diphenylhydantoin	↓/↓	↓	↓	↓	(-)
Lidocaine	↓/↓	↓	unknown	↓	( )
Propranolol	↓/↓	↓	↓	↓	--
Procainamide	↑/↑	↓	↓	↓	-
Quinidine	↑/↑	↓	↓	↓	--

*Symbols: ↑ = increase, ↓ = decrease; amplitude of arrow indicates relative degree of effect. ++ = strong positive effect; + = moderate positive

and to slowly increase this until conversion occurs. It is rare to require more than 25 Watt seconds in these patients. It is not necessary to administer general anesthesia or muscle relaxants to these patients since there is no generalized convulsive effect of this small shock. In some cases meperidine 1 mg per kilogram of body weight or diazepam 2 to 3 mg may be given for analgesia or relaxation. Once there has been a return to normal cardiac rhythm we digitalize our patients and maintain them on digoxin for 3 to 6 months since recurrences of the arrhythmia are frequent when it begins in the first year of life.

Children with the simple form of paroxysmal supraventricular tachycardia rarely present with critical illness accompanied by congestive heart failure. They are generally treated in sequence with diphenylhydantoin, propranolol, procainamide, and digoxin. In some cases only a combination of several of these drugs (e.g., digoxin and propranolol) will be successful. If none of these agents or combinations is effective, we prefer to use transvenous atrial pacing rather than direct current countershock as the next step in therapy. Some investigators feel that both of these procedures carry less risk than quinidine therapy.[11] The advantages of atrial pacing over the direct current countershock method are that there is no need for discontinuation of digoxin therapy and there is no need for general anesthesia. A transvenous bipolar catheter electrode can be inserted percutaneously without trouble and has the advantage that it can be left in place in case of frequent recurrences of the arrhythmia. The mechanism of atrial pacing and the effect of such a procedure upon the tachycardia have been reviewed in detail elsewhere.[1, 14]

Atrial pacing may convert a supraventricular tachycardia to a normal sinus rhythm by three different mechanisms. It may suppress an ectopic pacemaker through overdrive. It may convert a self-sustained tachycardia such as atrial flutter into one which is not sustained, such as fibrillation, which results in a return to sinus rhythm in many cases. The final

...tr pic ect	*Refractory period duration*			*Toxic effects*
	Atrial myocardium	*Ventricular myocardium*	*A V node*	
	↓	↓	↑	AV block arrhythmias g i tract symptoms
0	↓	↓	↑	Hypotension
0	0	0	0	Hypotension convulsions
–	↑	↑	↑	AV block hypotension
(+)	↑	↑	↓	AV block QRS widening hypotension
+	↑	↑	↓	QRS widening ventricular arrhythmias hypotension g i tract symptoms

... effect 0 = ... effect – = ... effect – = mod t neg ti ffect ( ) = min m l eg tl eff t

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All of these drugs were used in our patient at one time or another during his hospital course However they did not alter the activity of the ectopic pacemaker Following the use of pharmacotherapy it was decided to attempt atrial pacing in this

patient The atrial "overdrive" succeeded in returning him to a regular sinus rhythm only when it was combined with procainamide for the suppression of the ectopic focus The sinus rhythm was not stable, however, and he reverted to his arrhythmia soon thereafter

We decided to make a final attempt to convert his arrhythmia to a normal sinus rhythm, this time with high doses of quinidine High dosage quinidine therapy can be extremely hazardous and should be carried out only in an intensive care unit that is equipped and staffed for patient monitoring and resuscitation The use of serum quinidine concentration measurements to guide therapy does not eliminate the hazard of such a regimen since therapeutic effect and/or toxicity may not be predictable on the basis of serum level alone In our patient we assumed that the drug was absorbed completely as soon as a dose was given and that its half life in the body was 8 hours This approach permitted us to estimate the proper therapeutic regimen for him once the therapeutic range had been defined (Fig 1)

The authors are indebted to Miss Lucille M Rung and Mrs Leanore Rappaport for the preparation of these manuscripts

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Theoretic considerations of the post-systolic "dip" of constrictive pericarditis

Following its original description in 1946[1] various explanations have been offered for the presence of the post systolic dip (Fig 1) seen in pressure tracings recorded from the cavity of the right ventricle of patients with chronic constrictive pericarditis It has been suggested that the dip is an artifact produced by a low frequency recording apparatus[3] but the pattern has been found consistently in patients with constrictive pericarditis since high frequency recording equipment has become available Another explanation for the presence of the diastolic dip is that it represents an *actual cardiodynamic event*[3-5]—i e because the ventricles are completely empty at the end of systole and the atrial pressure is high rapid ventricular filling takes place which is abruptly terminated by the thickened pericardium However this theory does not explain why the ventricular relaxation is not isometric with time

Although the possibility of elastic recoil of the thickened pericardium and chest wall has been mentioned by some[6] a precise mechanism has not been offered We believe that a sudden to rather abrupt elastic recoil of the distorted (during systole) thickened pericardium when the ventricle rather suddenly relaxes is responsible for the diastolic dip in constrictive pericarditis and we therefore offer the following hypothesis

The heart in constrictive pericarditis is encased in a thick shell of fibrous connective tissue with or without calcium which is fixed to and therefore a part of the ventricular wall Thus when the ventricle contracts work is performed on this thick wall which deforms in much the same manner as when one loads a spring Following termination of myocardial contraction and with the sudden unloading of the distorted fibrous pericardium with the onset of diastole the ventricular wall abruptly springs back into place suddenly reducing intracavitary pressure thereby literally sucking blood from the atrium into the ventricle This recoil of the ventricular wall results in the rapid fall in ventricular pressure which is responsible for the ventricular diastolic dip recorded in the intracavitary pressure tracing The ventricle fills rapidly and therefore an early plateau of the right ventricular pressure tracing is seen (Fig 1)

Support of this concept is seen in experimental cardiac tamponade produced with air or fluid In such a situation the fluid or air in the pericardial cavity is not fixed to the myocardial wall even though diastolic filling of the ventricle is re-

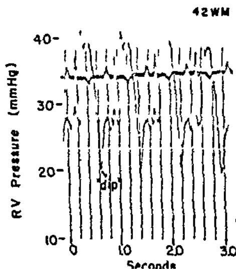


Fig 1 Time course of right ventricular pressure showing post-systolic dip in constrictive pericarditis

stricted Thus during systole there is no physiologic spring to load nor is there one to suddenly unload during the early phase of diastole Under such circumstances therefore the characteristic dip[4] in right ventricular pressure is not expected nor recorded[7]

Parenthetically it may be noted that the work performed in deforming the pericardium in constrictive pericarditis is not useful work and therefore myocardial contraction is less efficient and work and energy are wasted loading a physiologic spring This wasted work must contribute in part to the extra work of the heart which in turn contributes to early myocardial failure observed in patients with constrictive pericarditis

A possible comparison can be made between the heart in constrictive pericarditis and a heart with myocardial fibrosis in which the myocardium has been partially replaced by fibrous connective tissue In the latter heart the amount of contractile element has been reduced and/or the remainder diseased and in addition unnecessary work by an injured myocardium is required to deform the interstitial fibrous connective tissue The spring load concept is reflected in the right ventricular pressure

tracings from patients with such hearts which are similar to the tracings recorded from patients with constrictive pericarditis[8] The same concepts apply to hearts with endocardial fibrosis and thickening

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Blood flow in the internal mammary artery

Use of the internal mammary artery (IMA) as a coronary bypass graft has been criticized on the basis of its small caliber and limited flow capacity However a late failure rate as high as 30 per cent has been reported for saphenous vein in the first year[1,2] in contrast to three per cent for the IMA[3] Therefore in the past 10 months the IMA has been used 78 times for coronary bypass grafting

In most instances free graft flow was measured by a volumetric timed collection immediately prior to making the anastomosis After discontinuation of cardiopulmonary bypass IMA flow was measured using an electromagnetic flow probe Observations were made of basal flow of reactive hyperemia flow after a 30 second graft occlusion and of peak flow after injection of 15 mg of papaverine into the graft (Papaverine injection was performed in the first 34 grafts and then discontinued) This data is compared with flow data obtained in the standardized manner from a much larger series of saphenous vein coronary bypass grafts Free flow was not measured in the vein grafts (see Table I)

It is apparent that basal graft flows are similar for the IMA and saphenous vein whether to the right coronary artery (RCA) or to the left anterior descending artery (LAD) Both reactive hyperemia flow and peak flow are significantly less for the IMA These observations indicate that the flow

Table I Flow data for internal mammary artery bypass grafts compared to saphenous vein coronary bypass grafts

Variables	*Right IMA**	*Left IMA*	*Vein RCA*	*Vein LAD*
Number of grafts	17	51	185	213
Free flow (ml /min)	86 ± 9	98 ± 6	—	—
Mean arterial pressure (mm Hg)	84 ± 4	93 ± 3	—	—
Basal flow	68 ± 9	56 ± 4	61 ± 4	57 ± 3
Reactive hyperemia	68 ± 9	59 ± 4	86 ± 4	75 ± 4
Peak flow (papaverine)	79 ± 7	97 ± 9	174 ± 8	155 ± 7

*Abbreviations IMA = internal mammary artery graft RCA = right coronary artery graft LAD = left anterior descending artery graft

capacity of the IMA is limited and may not meet myocardial requirements t times of maximal need However the IMA is probably not at its ultimate caliber during the flow measurements Without question the IMA develops spasm during mobi iza tion and anti pasmodic agents such a Xylocaine or papaverine have not been used to remedy this Initially gentle balloon catheter dilation was used but thi resulted in intimal fracture in one graft and this maneuver was discontinued In three IMA grafts flow was remeasured ix to eight hours later at the time of reoperat on for postoperative hemor rhage At reoperation basal flow was 40 per cent greater than pre iously Vein graft flow has not been greater at reoperation This would indicate that the IMA dilates in the hours following operation and its flow capacity increases The lumenal diameter of the IMA has been 1 5 or 2 0 mm as measured with malleable probes in 0 5 mm gradations In only one n tance wa the IMA not used because of inade juate free flow and in this instance a hemostatic clip had been inadvertently placed across the artery at the first intercostal space

In the final analy is the apparent better long term patency of the IMA must be weighed against its limited flow capacity and the technical difficulties attending its use It is important to realize that once the sternum has been closed the IMA is lost since sternal closure may directly destroy it or secondary cicatrix precludes its future mobilization There fore the IMA cannot be held in reserve should saphenous vein coronary grafts fail but the IMA must be utilized at the initial operation if it is to be used at all

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Cell growth in man

If the object of the proce of education is to equip a child for adult l fe so the practice of pediatrics and especially the conduct of research in pediatrics mu t be chiefly concerned with the long term effects of disease proce se The prime function of the pediatrici n i to produce a healthy adult On the other hand diseases which u ually present in adult life probably have little chance of improvement if treatment is not in tituted early in life the long term treatment of males with Type 2 hyperlipopro te emia may be taken as an example of such a con d tion In childhood the basis of many pathogenetic proce ses i la d and environmental circumstances wh ch imp ge on the early l fe of a child may well carry l fe-long consequences

The effect of the en ironment on a developing org n m depend largely on timing Thus the effects of rubella on the eight week-old fetus are cata trophic wh t they are negligible on a eight year old ch ld It probable that the same principle applies to ill in ult It i pos ble for example to alter growth processe in animal experimentally simply by o er[1] or undern tr tion[2] ard in general the earlier the tre the more severe it effect Much f rmatin infor n tion on the brain growth of ani mals on these l ne ha accumulated and the indi cat on i th it u dernutr tion at certain cr tical per od can permanently reduce the number of bra n cell if the tres is of uff cient severity and d irat on Similar experiment have shown that mental develop ment may also be impaired

Experiments uch a these are clearly not pos ible in man It is known that head size can be affected by undernutrition during the period of most rapid brain growth in utero in the perinatal period[3] and in early childhood[4] In the latter study the reduction in head size of children dying of mara mus before the age of one year was directly related to the de crease in the number of brain cells Because of the difficulty in obtaining such data information hith erto available in man is scanty to say the least and it is not always justifiable to extrapolate directly from an mal experiments to the human situation

Body fat is unique as an organ in man in being ea ily sampled and relatively easily measured from skinfold thicknesses It appears in the fetus late in gestat on (at about 30 weeks) and its period of most rapid growth continues during the first year of post natal l fe In this organ it is therefore pos ible to study d rectly the effects of different environmental c rcumstances occurring in a period which is usually relatively well documented

I have studied the growth in the number of adi pose cells in children to whom a series of environ mental accidents have occurred Control values were obtained from otherwise healthy children under go ng elective surgery the other groups comprised one of obese children half of whom had gained weight excessively in the first year of life and half had not on of children with growth hormone de ficiency either idiopathic or following surgery for craniopharyngiomas and one of children whose birthweight was at least 2 SD below the mean after the length of ge tation had been allowed for

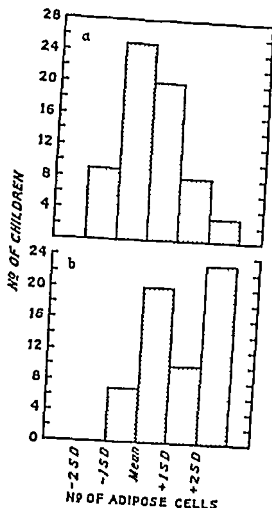


Fig *1* Total number of adipose cells *Panel a* control children *Panel b* obese children

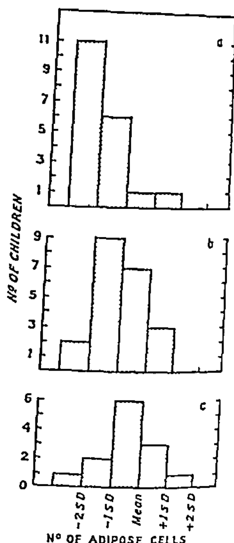


Fig *3* Effect of birth weight and growth hormone deficiency on the number of adipose cells in children *Panel a* light for their age children *Panel b* children with idiopathic isolated growth hormone deficiency *Panel c* children growth hormone deficient due to surgery for craniopharyngiomas

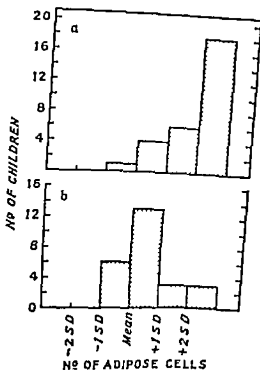


Fig *2* Effect of age at onset of obesity on the number of adipose cells in obese children *Panel a* early obese children *Panel b* later obese children

The number of adipose cells in obese children was increased (Fig 1) but the increase was entirely accounted for by the contribution made by the early obese children The later obese children though they were of similar fatness had a number of adipose cells which did not differ from control (Fig 2) Similar findings applied to a group of obese adults whom I have studied [7] Whether to have an increased number of adipose cells matters is not known but in view of the mortality rate and the morbidity associated with the condition it is a question which clearly demands an answer Since rapidly gaining babies also have an increased incidence of obesity later [8] it is more than of passing importance because it may be that we should reconsider our whole practice of infant feeding

In the growth hormone deficient and light for their age children the situation was the reverse (Fig 3) Light for their age children suffer a severe insult to adipose cell division early in the period of adipose organogenesis and have a profound deficit in cell number In children with idiopathic isolated

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rowth hormone deficiency the lack becomes oper tive presumably at birth later in organogenesis nd the cell deficit is less Children who lack growth ormone at a later stage would be expected to have assed the age when the adipose organ is sensitive o such circumstances These children would be xpected to have a normal complement of cells when he growth delay induced by growth hormone de iciency and evidenced by skeletal retardation is allowed for The findings in the group of children with craniopharyngiomas confirm this expectation

Thus the adipose organ it seems has a finite and well-defined sensitive period during which external circumstances have lasting effects on cellular growth Such a model presumably applies with different timings to all organs in man

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Serum enzyme levels after operation

The differential diagnosis of chest pain after operation is complicated by the fact that those serum enzymes which are characteristically elevated after myocardial infarction[1] (and to a lesser extent after pulmonary infarction) are also often raised post operatively[2] Therefore in order to establish the duration and extent of the serum enzyme level changes postoperatively serial measurements of aspartate transaminase (AsT) hydroxybutyric dehydrogenase (HBD) and creatine kinase (CK) levels were made after a variety of cold operations[3]

Fourteen patients undergoing thoracic or abdominal operations were studied having excluded those in whom the enzymes were elevated preoperatively those with abnormal electrocardiograms and those in whom there was any evidence of deep vein thrombosis or myocardial or pulmonary infarction Of the 14 patients, four underwent thoracotomy three cholecystectomy three vagotomy and pyloroplasty two partial gastrectomy one colectomy and one suprapubic prostatectomy The AsT and HBD levels were measured by spectrophotometric methods (normal ranges 4 to 15 and 50 to 150 I U per liter respectively) and the CK levels by a colorimetric method (normal range 4 to 60 I U per liter) The enzyme levels were measured preoperatively and at 24 hours three five seven and 10 days postoperatively

In 10 patients there was an elevation of all three enzymes maximum levels being attained at 24 hours or three days after which they gradually fell to normal levels The highest levels recorded were AsT 62 I U per liter HBD 406 I U per liter and CK 550 I U per liter These figures are within the range of enzyme results frequently encountered after myocardial infarction[1] In every case in this series the HBD had returned to normal within five days of operation the CK within seven days and the AsT was normal in most patients by 10 days at which time all AsT levels were below 20 I U per liter

The rises in serum enzyme levels after operation are probably due to trauma to tissues especially skeletal muscle[3] This is supported by the finding that the highest enzyme rises occurred after operations involving the most extensive operative trauma (thoracotomy patients)[3]

Elevated serum enzyme levels after operation must therefore be interpreted with extreme caution After the fifth postoperative day the significance of raised serum enzyme levels increases with respect to the diagnosis of postoperative myocardial or pulmonary infarction Elevated levels after the tenth

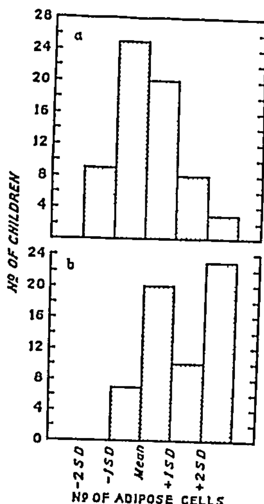


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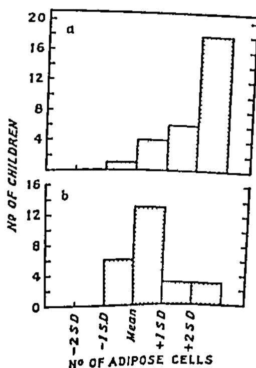


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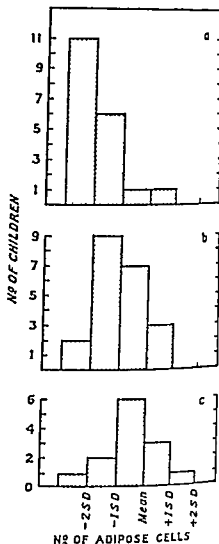


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postoperative day can no longer by attributed to operative trauma

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Book reviews

SCLERODERMA Proceeding of an International Sym posium sponsored by the World Health Organiza tion Edited by Prof F Delbarre Paris 1972 Masson et Cie 311 pp

Thi series of papers represent the proceedings of a symposium sponsored by the Wo ld Health Or ganization The papers are in French or English This book is concerned with seven main subjects namely general aspects of scleroderma sclero-derma as a cutaneous disease scleroderma as a systematic disease the clinical forms diagnostic problem anatomic and pathologic changes and treatment In essence this is a summary of the practical clinical problems of scleroderma a some-what rare but important disease This review is a good one and the book certainly is useful in that it contains the important aspects of the problems of scleroderma presented for the clinician Doc tors will find this to be an excellent review of the subject

ADVANCES IN CARDIOLOGY Early Diagnosis of Coro-nary Heart Disease P Halonen and A Louhija Editors Helsinki Basel Munchen Paris London New York Sydney 1973 S Karger AG 231 pp Price $24 20

This important book describes the present day idea on the early diagnosis of coronary heart disease It really contains nothing especially new but it brings together for readers the concepts of clini cians concerning the r own experience with the early diagnosis of coronary heart disease The book is certainly worth owning and studying Coronary arteriography emotional factors hyper lipemia apexcardiography atrial pacing mea surements of coronary flow prevention and early diagnosis are among the many subjects discussed Thi is a useful book for valuable reading by those with l mited time

BLOOD FLOW MEASUREMENT Edited by Colin Roberts Baltimore 1972 The W lliams & Wilkins Company 184 pp Price $18 75

Dr Roberts has edited a book which is concerned briefly with aspects of the methods and tech niques for measuring blood flow in the heart and large blood vessels The peripheral flow such as in the d gits and microcirculation is neglected Each presentation of which there are 34 in 181 pages can attest to the brevity of each discussion Nev ertheless those who are seriously engaged in studying and measuring blood flow w ll find th s book interest ng The problems difficulties and inaccur cies of the various techn ques are not criti cally discussed This would not be expected in thi mall book The book is well written and clearly presented so that readers can learn the methods and principles involved in measuring blood flow in large vessels

ANTIARRHYTHMIC AGENTS Arthur J Moss M D and Robert D Patton M D Springfield Ill 1973 Charles C Thomas Publisher 161 pp

Moss and Patton have produced a book which is concerned primarily with ten antiarrhythmic agents commonly used in medicine at present The electrophysiology of the heart is briefly de-scribed and the pharmacology and clinical use of the antiarrhythmic agents presented in separate chapters The entire book contains only 112 pages and therefore would not be expected to contain detailed information about these drugs. The authors have presented their own concepts in management briefly Readers will find this to be a short quick source of data on important drugs.

MYOCARDIAL BLOOD FLOW IN MAN Methods and Significance in Coronary Disease A Maseri M D Editor Turin 1972 Minerva Medica 576 pp Price $35 00

This book contains the papers and discussions on Myocardial Blood Flow in Man presented at a meeting in Pisa during June 10 to 12 1971 The participants were from many nations and the subjects discussed were quite varied The book is divided into six parts and a round table discussion The six parts were concerned with determinants of myocardial blood flow trans-mural distribution theoretical and technical problems hemodynamic correlates significance of measurements adaptations to ischemia and adaptations of myocardial perfusion to coronary artery disease Discussions follow most of the papers A considerable number of problems are discussed They are of importance and should interest physiologists and cardiologists since ischemic heart disease is so common In spite of the extensive stud es in progress it is still not possible to measure quantitatively the rate of coronary blood flow with sufficient accuracy and sensitivity to meet the needs required to supple-ment the clinical data already obtainable The procedures available for intact man are too com plex and insensitive to be of practical value This is evident from this book Nevertheless this is an important publication which should interest cardiologists and physiologists The organizing group for the symposium has done a fine service to cardiology

Announcements

American Institute of Ultrasound Meeting

The Eighteenth Annual Meeting of The American Institute of Ultrasound in Medicine will be held in Ann Arbor Mich October 14 through 18 1973 The program will include a full day of educational lectures and video tape on all disciplines in medicine

For further information regarding this meeting please contact Dr Michael A Wainstock Towsley Center University of Michigan Medical Center Ann Arbor Mich 48104

Postgraduate course in angiography

The second postgraduate course in Advances in Angiography Technical Equipment Clinical—Phase II will be held January 30 through February 1 1974 at the Sands Hotel Las Vegas Nevada The course is sponsored by the Departments of Radiology of Shadyside Hospital in conjunction with the University of Pittsburgh School of Medicine The course is intended for radiologists cardiologists and other personnel involved in vascular examinations Panel discussions by manufacturers leading investigators will be correlated with clinical comments by prominent clinicians actively involved in vascular examinations The course will emphasize personal opinions regarding all aspects of arteriography Registration fee is $90 (Registration is limited to 500 on a first enrollment basis) Persons wishing further information may write to Shadyside Hospital Radiology Seminar Department of Radiology 5230 Centre Ave Pittsburgh Pa 15232

Symposium on diagnosis and management of hypertensive patients

The University of Texas Health Science Center at Houston Medical School and Division of Continuing Education will present a brief review of new developments in the diagnosis and management of the hypertensive patient on November 29 1973 The symposium will be held in the Auditorium of the Jesse H Jones Library Building at Houston Texas

Recognizing that important developments have occurred recently to help the physician diagnose and treat the hypertensive patient this program has been organized It is designed to help the physician properly apply this new information and also to extend logically information concerning antihypertensive drug therapy to those who have a reasonable chance of benefiting from it The faculty drawn from across the country will address itself to these problems and offer acceptable solutions to the practicing physician

Program director for the symposium is Walter M Kirkendall M D Professor and Director Program in Internal Medicine The University of Texas Health Science Center at Houston Medical School The registration fee is $15 including luncheon and handout material

For further information regarding this program please write Office of the Director The University of Texas Health Science Center at Houston Division of Continuing Education P O Box 20367 Houston Texas 77025

American Heart Journal

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Editorial

Cyclophosphamide and the treatment of the nephrotic syndrome in adults

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It is more than 20 years since the publication of the first reports on the use of mechlorethamine (nitrogen mustard) in the treatment of patients with glomerulonephritis [1,2] However the difficulties associated with its use and the introduction of corticosteroid therapy reduced interest in the alkylating agents for a decade while the limitations and dangers of steroids were appreciated By this time new drugs such as cyclophosphamide and chlorambucil which were less toxic than nitrogen mustard and which could be given orally had been introduced and in 1963 the first report of the use of cyclophosphamide in the treatment of children with the nephrotic syndrome was published [3] This report dealt largely with patients suffering from minimal change lesions and although cyclophosphamide has since been used in patients with other renal lesions the great majority of evidence about its value in the treatment of patients with the nephrotic syndrome still concerns this group

Minimal change lesion

Patients suffering from this condition which is also known as lipoid nephrosis usually have a pure nephrotic syndrome without hematuria or hypertension The great majority are children but something like 30 per cent of adults with the nephrotic syndrome may also show this appearance [4] Examination of biopsy material reveals normal or near normal glomeruli without deposition of immune globulins or changes in the glomerular basement membranes Usually the condition runs an intermittent course with remissions and relapses occurring spontaneously[5] or in response to treatment with corticosteroids In order to maintain remission many patients require continuous therapy with steroids in doses which produce severe side effects This problem is greatest in children in whom suppression of growth is added to the other well known problems of treatment

A large number of papers have now been published[6-10] which provide ample evidence that cyclophosphamide is able to induce remission of the nephrotic syndrome in children with this condition It seemed that these remissions lasted longer than those formerly induced with steroids[10] and in 1970 Barratt and Soothill[11] confirmed by means of a controlled trial that this was in fact the case Patients do still relapse however and it is probable that only in about 50 per cent is permanent remission achieved [12,13] Even a temporary result is

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however, well worth having at the least the stigmata of steroid toxicity are given time to regress and growth in height is achieved Although no trial has been reported which compares cyclophosphamide with azathioprine, the poor results obtained using the latter drug[14] suggest that cyclophosphamide is much superior Cyclophosphamide may either be given alone[10] or during a remission which has been induced and maintained by steroids [11,12] Currently we are using an eight week course of treatment in a dosage of 3 mg per kilogram of body weight per day and have no evidence that larger doses or longer courses influence the long term outlook [12,13]

There is much less evidence available about the place of cyclophosphamide in the treatment of adults with minimal renal lesions This is partly because of the relative rarity of the lesion in this group[4] but also because the toxicity of steroids in adults is often not as great as it is in children However the evidence that is available suggests that the situation in adults is no different from that in children [15,16] Initial response may be anticipated in the vast majority of patients but again relapse may occur eventually [16]

Occasional patients with biopsies showing minimal renal lesions fail to respond to treatment with steroids A proportion of these do respond to cyclophosphamide[15] but the majority do not Many of these patients are probably suffering from a different condition focal glomerulosclerosis which affects initially only the juxta medullary glomeruli which may not be present in a biopsy containing only renal cortex Response of patients with this condition to cyclophosphamide is unusual[17,18] although not unheard of [19]

Systemic lupus erythematosus

Work on two animal models of this condition namely the F1 hybrid of the NZB and NZW mouse[20,21] and Aleutian disease of mink[22] in which the animals normally develop a severe proliferative glomerulonephritis has shown that treatment with cyclophosphamide can either slow the progression of the renal disease or prevent its appearance completely This has provided a rational basis for the use of this drug in the treatment of the nephrotic syndrome associated with systemic lupus erythematosus in man Initial uncontrolled reports[3,24] gave promising results and recently a controlled trial[25] has produced clear-cut evidence that cyclophosphamide does have a place in the treatment of these patients The ideal dose regimen has not yet been established and it is not yet clear that cyclophosphamide is superior to for instance azathioprine and steroids given in combination

The drug may also have a place in the treatment of other systemic disorders with renal involvement such as Wegener s granulomatosis [26] but we have been unimpressed with its efficacy in the treatment of the nephrotic syndrome associated with Schonlein Henoch purpura [27]

Proliferative glomerulonephritis

The majority of adults with the nephrotic syndrome suffer from one or other of the many subtypes of this condition A common classification, which has been outlined by Cameron[28] includes endothelial proliferative nephritis rapidly progressive nephritis with crescents, and mesangiocapillary glomerulonephritis It is likely that even these subgroups are heterogeneous and it is not surprising that there is no clear-cut information about the role of cyclophosphamide in the treatment of these conditions Most patients with the nephrotic syndrome due to proliferative nephritis run a downhill course to renal failure over a period of 10 to 20 years[13] and it would be naive to expect relatively short courses of treatment to achieve more than arrest or slowing of progressive renal functional impairment However the success of treatment with cyclophosphamide in patients with systemic lupus erythematosus who may show any of these lesions in their renal biopsies provides a continual stimulus towards evaluation of this drug in patients with proliferative nephritis

We [29] and others,[30] have treated isolated patients with mesangiocapillary glomerulonephritis with variable but generally unimpressive results while Kincaid Smith and colleagues[31] have compared patients treated with cyclophosphamide and anticoagulants together with patients receiving no treatment and showed that the treated group fared better [31] Patients with biopsies

showing multiple crescents fail likewise to respond to cyclophosphamide alone[32] but recently we have used this drug in combination with anticoagulants and steroids with encouraging results[33]

Membranous nephropathy

The incidence of this lesion among adults with the nephrotic syndrome is variable but in the United Kingdom it accounts for roughly 12 per cent of the cases[4] Again patients run a steady downhill course to renal failure over a period of about ten years[13] There have been very few reports of the use of cyclophosphamide in this condition but recently Donadio[34] has discussed the result of a small controlled trial which failed to demonstrate any benefit from treatment with this drug Again however the suggestion that this condition may well have its origin in an immunological disorder as shown by its production in experimental animals[35] and by its occasional appearance in patients with systemic lupus erythematosus should encourage continued interest in therapy with immunosuppressive agents

Toxicity of cyclophosphamide

The dangers of therapy with cyclophosphamide should not be underestimated Formerly it was believed that most of the toxicity was reversible and avoidable by careful supervision of the patient with regular checks on the blood count Nonetheless many patients suffered nausea and alopecia and some died from overwhelming sepsis[36] Recently however it has been appreciated that permanent damage may be produced to the bladder and to the gonads Chemical cystitis is a well recognized acute side effect of treatment but it has now been realized that the drug can cause fibrosis of the bladder wall[37] and possibly also bladder tumors[38] More serious however is the suggestion that cyclophosphamide may cause permanent sterility Earlier this year Fairley and colleagues[39] reported the results of analysis of seminal fluid from 31 men who had received cyclophosphamide All showed low or absent sperm counts and testicular biopsy in five showed absent or minimal spermatogenesis Similar results were obtained by Kumar and colleagues[40] from Belfast and there seems little doubt that cyclophosphamide can cause profound and possibly permanent damage to the adult male testis The danger of treatment given before puberty is less certain Berry[41] was unable to demonstrate any major effect on the subsequent reproductive function of male rats treated with cyclophosphamide before sexual maturation For obvious reasons there is a paucity of information in boys and in particular there is very little histological information One boy with Hodgkin s disease who had radiotherapy in addition to 3 months cyclophosphamide was found to have severe testicular atrophy when he died later[42] However we found (unpublished data) normal testes in one child aged 6 years at death who had received 8 Gm of cyclophosphamide over a 180 day period two years previously and Arneil (personal communication) has collected information on the testes of 15 prepubertal boys treated with cyclophosphamide for malignant disease All were normal except one who had in addition received radiotherapy for his Hodgkin s disease However Etteldorf[43] has studied 5 men who had received cyclophosphamide during childhood and showed azoospermia in three who had received this drug 6½ 8 and 12 years before Two of his patients who 8 and 11 years previously had received short courses similar to those now recommended for the treatment of children with the nephrotic syndrome due to minimal renal lesions had satisfactory sperm counts West[19] has seen three men who had received cyclophosphamide in childhood and subsequently fathered children who were normal and it seems that the occurrence of long term testicular damage is dependent on the total dose employed

Evidence also exists that cyclophosphamide may damage the ovary Women receiving the drug for more than six months regularly develop amenorrhea[40,44] which may be associated with a low urinary excretion of estrogen and a high urinary excretion of gonadotrophin[44] suggesting that cessation of menstruation is due to ovarian failure However menstruation usually returns when the drug is withdrawn[45] and patients have even become pregnant while receiving the drug[46,47] Pregnancies have

been terminated in two of our own patients who became pregnant while taking cyclophosphamide. This policy was adopted as much for psychosocial as for medical reasons although there is some evidence that cyclophosphamide might be teratogenic in these circumstances.[46,47] We (unpublished data) have seen two normal pregnancies following short courses of cyclophosphamide and this has also been the experience of others.[48]

Conclusion

The recognition of the long term effects of cyclophosphamide on the gonads has prompted some revision of ideas about its place in the treatment of patients with the nephrotic syndrome. The drug is most effective in those patients who do best on corticosteroids; hence it should only be given to patients with minimal lesions who experience severe side effects from corticosteroids. Even then it should only be given in short courses, particularly when dealing with male patients. In patients with progressive and potentially lethal renal disease the risk of sterility is probably justified provided that the drug can be shown to be more effective than other less toxic agents.

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Clinical communications

Early systolic notch in the apexcardiogram in mitral stenosis

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An early systolic notch on the upstroke of the apexcardiogram (ACG) has been considered a useful diagnostic sign of mobile left atrial myxoma [1-5] The notch is thought to be caused by movement of the tumor from left ventricle to left atrium in early systole [2] Although a small notch in the ACG may sometimes be seen in normal subjects [6,7] it has not been reported to occur in mitral valve stenosis

During evaluation of a patient (K E) with auscultatory signs of mitral stenosis an ACG was recorded with an early systolic notch However an echocardiogram demonstrated the typical findings of mitral valve stenosis and no myxoma this was confirmed at surgery Subsequently three additional patients have been found with valvular mitral stenosis in whom an early systolic notch has been recorded

Methods

Apexcardiograms were obtained by manually holding a 25 mm funnel applicator attached by a 6 cm length of plastic tubing to an air filled Statham 23Db strain gauge on the apical impulse The patient was most often in the left lateral position but sometimes was supine The signal was amplified by a Hewlett Packard 350 100 C preamplifier and recorded at 75 mm per second on a Hewlett Packard 4560 Photographic recorder The damped natural frequency of this system was 83 cycles per second determined by a balloon rupture technique [8] Simultaneous electrocardiograms (Lead II) and phonocardiograms (lower frequency cut off of 200 Hz) were also recorded

The preoperative apexcardiograms of all patients who had undergone mitral commissurotomy for relief of mitral stenosis in 1970 through 1971 were reviewed in a retrospective fashion In these patients no special attempt had been made to record a notch Of 23 patients who underwent mitral commissurotomy in 1970 through 1971 16 had ACG s and 12 were technically adequate

In addition the next three patients with pure mitral stenosis proved by catheterization seen in our institution had ACG s in which a definite effort was made to manipulate the funnel over the cardiac apex to

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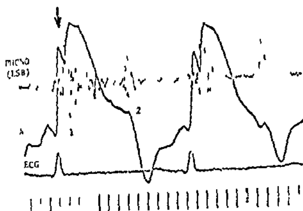


Fig *1* Simultaneous apexcardiogram (*ACG*) left sternal border phonocardiogram (*PHONO*) and Lead II electrocardiogram (*ECG*) are shown for patient E E The first (*1*) and second (*2*) heart sounds are labelled The prominent notch interrupting the systolic upstroke of the ACG is indicated by an arrow Time lines at the bottom of the figure are 04 second apart

produce an early systolic notch The ACG was technically satisfactory in two and unsatisfactory in one Our original patient (K E) was considered in the prospective group because myxoma was being actively considered at the time of study

Results

An early systolic notch was seen in two of the twelve adequate ACGs in the retrospective group and in two of the three adequate ACGs in the prospective group Table I presents the clinical data on these four patients and their ACGs are shown in Figs 1 to 4 A prominent notch on the upstroke of the ACG is seen in each of these records In three patients (E E K E and R P) the notch coincides with the first heart sound In the other patient (E S) the notch follows the onset of the first heart sound by 0 03 sec

The way the pickup was held on the cardiac apex seemed to affect significantly the shape of the ACG and the presence of the early systolic notch Fig 4 illustrates the ACG obtained in patient K E with the funnel held on the apex in two slightly different positions

Discussion

Previous reports dealing with the ACG in mitral stenosis[9,10] have been concerned with the diastolic portion of the recording or with the timing of sounds in the cardiac cycle However one of these published ACGs demonstrates early systolic notching (Ref 9 Fig 5)

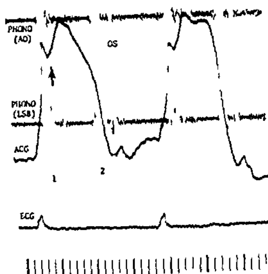


Fig *2* Patient E S *PHONO (AO)* indicates phonocardiogram in aortic area and *OS* indicates opening snap Other abbreviations as in Fig *1*

There are probably several causes of an early systolic notch in the ACG In some cases the notch may merely represent an artifact of recording The variability of the systolic portion of the ACG has been previously noted[6,11] and others have pointed out that marked alterations in the shape of

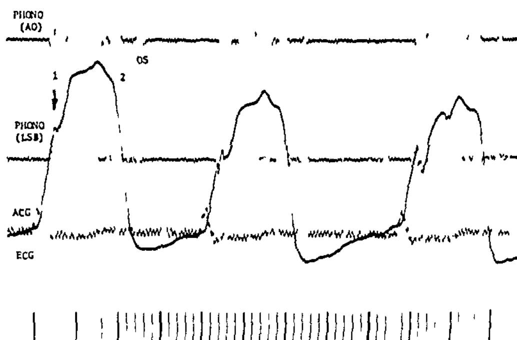


Fig 3 Patient R P For abbreviations see Figs *1* and *2* Note that the patient is in atrial fibrillation and that the early systolic notch is variable In a longer record there was no relation between the cycle length and the prominence of the notch

Table I Clinical data on 4 patients

Patient	*Age (yr)*	*Sex*	*MMG*	*Associated disease*	*Cardiac rhythm*	*How discovered*	*Catheterization†*	*Surgery†*	*Q-S₁‡*
E E	49	F	12	Mild AR	NSR	Retrospective	+	+	08
E S	56	F	12	Mild AR	AF	Retrospective	+	+	08
K E	25	F	—	Pregnant	NSR	Prospective	−	+	10
R P	53	M	8	Mild AS moderate AR	AF	Prospective	+	−	09

*Abbreviations MMG = mean mitral valve gradient (mm Hg) at cardiac catheterization AR = aortic regurgitation AS = aortic stenosis NSR = normal sinus rhythm AF = atrial fibrillation

†Catheterization and Surgery columns indicate how atrial myxoma was excluded in each patient All patients had mitral valve surgery only

‡Q S_1 = interval in seconds between the onset of the Q wave in the Lead II ECG and the first high frequency component of the first heart sound in the phonocardiogram Values of Q S_1 for normals or patients without mitral valve disease are less than 0 06 sec[14,15]

the systolic waves may occur with slight changes in the position of the recording device[7,11,13] One of our patients (Fig 4) illustrates that an early systolic notch may be brought out by careful manipulation of the funnel applicator

In patients with valvular mitral stenosis the notch may reflect the loud first heart sound It has been shown that there is frequently a prolongation of the interval from the Q wave of the ECG to the onset of the first heart sound in mitral stenosis[14,15] This prolonged 'Q S_1 interval' is thought to be due to the greater time required for left ventricular pressure to rise above left atrial pressure Because of the delayed onset of S_1 its low frequency vibrations would occur later on the systolic upstroke of the ACG than normally and might produce a more noticeable distortion

Our data supports this latter hypothesis since all our patients had prolonged Q S_1 intervals and increased intensity of the first sound The notches on the ACG coincided with the S_1 in three of the patients while in the fourth patient the notch followed the

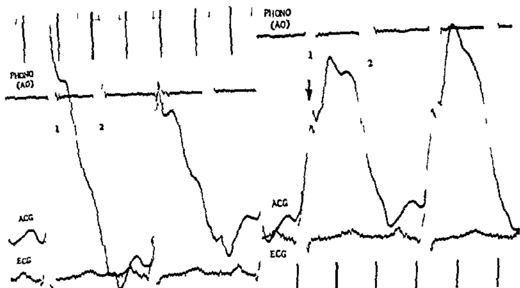


Fig 4 Patient K E For abbreviations see Figs 1 and 2 *Left panel* shows ACG taken in routine fashion *Right panel* demonstrates the appearance of a prominent notch after slight movement of the pickup funnel over the cardiac apex

onset of S_1 by 0 05 second We have no explanation for this discrepancy in the fourth patient

Although an early systolic notch in the ACG in patients with clinical sign of mitral valve obstruction has been shown to be non pecific we feel that it should still alert one to the possibility of myxoma and that further investigation should be per formed Ultrasound may be used to exam ine the echoes from the mitral valve ap paratus or echoes from a myxoma tumor mass of the left atrium [16,17] If an early systolic notch in the ACG is found in a patient in whom myxoma is a possibility trans septal puncture of the left atrium should not be done without first visualizing the left atrium during the levo phase of a pulmonary arteriogram

Summary

An early systolic notch on the upstroke of the apexcardiogram (ACG) has pre viously been reported to occur in mobile left atrial myxoma but has not been noted in valvular mitral s enosis It has therefore been considered a useful diagnostic sign for myxoma We report four patients with mitral valve stenosis who had an early systolic notch in the ACG Myxoma was excluded by catheterization and/or surgery We feel that the notch is not specific for myxoma and that its finding should be interpreted with caution

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An analysis of deaths occurring in association with coronary arteriography

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In the course of a continuing Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease, a system of reporting on coronary arteriograms performed by 18 cooperating hospitals since June 1968 was established. These arteriography logs also carried data concerning deaths occurring in association with the procedure. The opportunity thus presented itself of analyzing these data both for incidence and cause of fatalities by reviewing the records and coronary arteriograms of all patients who were reported to us as having died within 10 days of the angiographic procedure. It seemed important to do this because heretofore coronary arteriography has often been reported as being associated with a very low risk.[1-5] Recent reports in the medical literature and our own data do not bear this out.[6-11] We also hoped that preventive measures might be developed if some of the mechanisms of death appeared to be avoidable.

Not all of the 18 participating hospitals were involved in the Cooperative Study for the entire duration of the time span encompassed by this report (June 1968 through June 1972). In addition, three other hospitals not participating in the Study contributed cases. Since the arteriography logs did not require information regarding the technique of coronary arteriography which was employed, this was sought retrospectively by questionnaire from each participating hospital; these data are therefore approximations.

Methods

The clinical records, coronary arteriograms, catheterization data, and autopsy reports for all patients reported to have died were reviewed and analyzed. All available coronary arteriograms were personally reviewed. Histopathologic sections of coronary arteries of selected patients were also reviewed. Clinical and autopsy data were tabulated and an attempt was made to correlate the results.

Results

Sixty-six deaths were available for analysis from 16 of the 18 cooperating hospitals. Sixty-four of these were reported from a total of 3,044 arteriograms performed by 17 of these hospitals between June 1, 1968, and June 30, 1972. The incidence of fatalities occurring within 10 days

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of coronary arteriography in these hospitals was thus 2.1 per cent.

All of the 66 patients who died were men, 62 of them between 40 and 60 years of age. Four were over 60. There were 56 white, 9 black, and one native Indian patients. The indication for coronary arteriography was angina pectoris in a patient who was considered a potential candidate for surgery for this symptom in 44 cases. In most instances, angina was of many months' duration. Uncertainty of diagnosis in a patient with atypical chest pain was the indication for arteriography in six, congestive failure or cardiomegaly in four, and postoperative follow-up studies were the indications in eight. In four instances the precise indication was not clear from the record. Only five patients had no angina. There was a history of myocardial infarction in 41 patients (60 per cent) and electrocardiographic evidence of old infarct, myocardial ischemia, or a positive stress test in 52 (76 per cent).

Left ventriculography was reported as having been performed in 42 patients; there was some abnormality of size, contractility, or ejection fraction in 24 of these (57 per cent). Significant coronary occlusive lesions (narrowing of lumen diameter of 50 per cent or greater) were noted (either on angiograms or at autopsy, or both) in all but two patients in this series. In 11 patients the left main coronary artery was significantly stenosed at angiography, and in 31 of 47 in whom coronary angiography had been completed, three or more major vessels were involved with significant lesions. Thus most of the patients who died had significant diffuse disease and the majority also had subnormal left ventricular function.

Forty-nine patients (74 per cent) died within 24 hours of the completion of the procedure—26 of them (39 per cent) within three hours. We included in this report all deaths reported to us which occurred within 10 days of coronary arteriography.

The exact incidence of fatalities in association with coronary arteriography was difficult to determine for several reasons: (1) arteriography logs were not kept by two hospitals, (2) data on the techniques used in the 3,044 arteriograms were obtained retrospectively and were imprecise, and (3) there were 13 deaths in patients not registered on the arteriography logs. This occurred because only the names of those patients who underwent coronary arteriography in connection with the Cooperative Study were required to be entered on the logs.

However, precise data about the techniques used in the fatal cases was available in every instance. Based upon these, there were two deaths* (0.3 per cent) in approximately 750 arteriograms using the transbrachial approach and 51 deaths (2.2 per cent) in approximately 2,300 arteriograms using the transfemoral approach.†

An attempt was made to classify all deaths in accordance with the best available information.

The largest group of deaths (Group 1) (35/66 or 53 per cent) was attributable to acute coronary occlusion, based either on angiographic evidence of sudden occlusion of a previously patent coronary artery (Fig. 1*A* and *B*) or pathologic evidence of a fresh occlusive lesion in a major coronary artery (Fig. 2*A* and *B*), or both. Of this group, 28/35 or 80 per cent of the patients died within six hours and five within two days; the remaining two patients died at intervals of three and nine days. In 12 of these patients an acute myocardial infarction was noted at autopsy in addition to the occlusive lesion. In 15 of these patients an embolus with a unique histological appearance was identified.[13] In all but four instances the left coronary artery was being catheterized at the time of the acute episode.

Eight patients (Group 2), all of whom died within 24 hours of angiography, were classified as having had an acute cardiac arrhythmia. In none of these patients was an acute myocardial infarction or an acutely occluding coronary arterial lesion identified.

In six patients (Group 3) an acute myocardial infarction was found at autopsy without evidence of an acutely occluding

*In an earlier report three deaths were recorded with the transbrachial technique.[12] One of these was from a non-VA Hospital; the arteriographic volume of this hospital was not used to calculate incidence and this death is therefore omitted from this calculation.

†$p < .001$



Fig. 1. *A* and *B*. *A*, Complete occlusion of the left main coronary artery by embolus (*arrow*). Moments before during left ventriculography, this vessel was seen to be patent. *B*, Complete occlusion of distal right coronary artery by embolus (*arrow*). On a previous injection of this vessel a few moments earlier, the distal right coronary was seen to be patent.

Table I. Incidence of fatalities in association with coronary arteriography

		Number of patients	*Per cent deaths*
1	Ross and Gorlin,[4] Am. Heart Assoc. study (80% Cleveland Clinic) 1968	3,312	0.1
2	Kasparian and Lebman,[5] 1967	800	0.3
3	Kaltenbach and Lichtlen,[10] 1971	1,[illegible]98	0.6
4	Selzer, Anderson, March,[9] 1971 — San Francisco area	2,2[illegible]5	0.9
	Selzer, Anderson, March,[9] 1971 — Another Western city	800	[illegible].6
5	Chahine, Herman, Gorlin,[7] 1972	891	1.0
6	Adams, Fraser, Abrams,[11] 1972	46,900	0.44
7	V.A. Coop Study (up to 10 days) 1972	3,044	2.1

arterial lesion either at angiography or at autopsy. Most of these patients (5/6) lived for 12 hours or more (up to 10 days) after the completion of the procedure.

Four patients (Group 4) died of the consequences of a cerebrovascular accident which occurred during the procedure. These patients lived from two to nine days after angiography. Four (Group 5) died in association with problems relating to the femoral arterial puncture, three of them less than 24 hours after the angiographic procedure. One patient (Group 6) died four days after angiography of an acute septicemia, and in eight instances (Group 7) no specific mechanism for death could be identified.

All but one of the 53 patients in Groups 1 to 4 had had at least one change of catheters prior to the acute episode, and many had two, three, or more changes of catheters. In three instances the fatal episode occurred after change of catheters but prior to the injection of any contrast medium. In seven patients, the fatal episode occurred after only a small test injection in or near the orifice of the left coronary artery. In many instances prior to the fatal episode, episodes of hypotension or concomitant or associated studies had delayed or prolonged the procedure.

An analysis of more complete data available from a subset of 1,295 patients from arteriography logs, to determine the risk of arteriography in those with significant stenotic lesions of the left main coronary

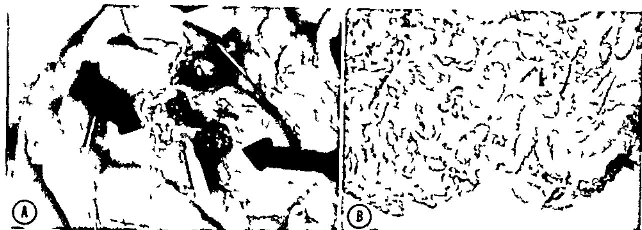


Fig 2 A and B A Autopsy specimen showing cut left main coronary artery near its orifice The lumen is completely occluded by fresh thrombus B Histologic section showing friable coiled platelet material found in this coronary artery (Hematoxylin and eosin Original magnification ×25)

Table II Classification of deaths (66 cases)

	No	Per cent
1 Acute coronary occlusion	35	56
2 Acute arrhythmia	8	12
3 Acute myocardial infarction	6	9
4 Cerebral vascular accident	4	6
5 Problems related to arteriotomy	4	6
6 Acute septicemia	1	1 5
7 Non specific or unidentified	8	12

Table III Acute coronary occlusion in association with coronary arteriography

	No
Fresh thrombosis described at autopsy	26
(catheter embolus identified)	(15)
Acute hemorrhage into atheromatous plaque	2
Acute coronary arterial subintimal dissection	1
Angiographic evidence only	6

artery was possible In this subset there were 125 patients with significant lesions of the left main—eight of whom died in association with arteriography (6 4 per cent) This compares with 26 deaths from among the remaining 1,170 patients without left main coronary artery lesions (2 2 per cent) ($p < 0\ 01$)

Discussion

The incidence of fatal complications was so low earlier using the transbrachial technique that coronary arteriography quickly gained acceptance as a relatively safe diagnostic procedure [1,5,14] However, more recently there has been an unmistakable increase in the incidence of fatal complications which seems to be related to increasing use of the transfemoral approach [6,11]

The disparity between the fatal complication rates of the two techniques has been noted by several authors [7,10,44] For example Chahine and associates[7] reported no deaths in 413 studies using a brachial arteriotomy and a 2 per cent incidence of fatal complications among 478 studies using the transfemoral technique There is little doubt that the transfemoral method has been easier to teach and to learn since it utilized the familiar Seldinger technique for gaining access to the femoral artery and preformed easily guided catheters were used [2,3] The complications involving brachial arteriotomy which can be substantial even in good hands could be avoided by using the transfemoral technique [15] It seemed to be merely a simple extension of the very useful technique of selective catheterization of the branches of the abdominal aorta

Unfortunately in the ascending aorta, and with multiple changes of catheters the problem is more complex and the procedure can be more dangerous The explanation for the disparity between the fatal complication rates following transbrachial and transfemoral coronary arteriography seems to be related to the mechanism of sudden coronary arterial occlusion due to

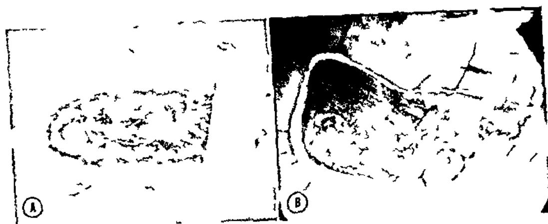


Fig. 3. *A* and *B*. Examples of coronary arterial emboli from two patients who died in association with coronary arteriography. Note characteristic appearance of coiled masses of platelets with few red cells and little fibrin in an artery with little evidence of severe atherosclerosis. (Hematoxylin and eosin. Original magnification ×25.)

Table IV. Influence of technique on mortality

	Transbrachial		*Transfemoral*	
	No. of patients	*Incidence*	*No. of patients*	*Incidence*
Kaltenbach and Lichtlen[1] (1971)	1,367	0.4%	431	0.9%
Chahine, Herman, Gorlin[7] (1972)	413	0.0%	478	2.0%
VA Coop Study (1972)	750	0.3%	2,300	2.2%

emboli from guidewires or catheters. As will be noted, the guidewire is the essential element in this mechanism and guidewires are not ordinarily used in the transbrachial technique.

In a previous report[12] 26 patients were reported who had died in association with coronary arteriography and in whom evidence of acute coronary occlusion was found. Catheter embolism was the postulated mechanism in many instances. In a subsequent report[13] it was shown that catheter emboli could be identified by their unique and characteristic histologic appearance which was completely unlike that seen with in situ thrombi found in some cases of sudden death from coronary arterial disease.

Since our initial report, nine additional cases of acute coronary occlusion apparently due to this mechanism have been contributed by participating hospitals. The characteristic histologic appearance of these emboli is attributed to the way they are thought to have developed (Fig. 3*A* and *B*). It is known that fibrin and platelets begin to adhere to the surfaces of catheters and presumably of guidewires (if the transfemoral technique is being employed) very soon after these foreign objects are exposed to the blood stream.[16-20] In removing a guidewire from a catheter, this fine layer of platelets is easily stripped from the wire by the closely fitting catheter tip and may adhere to the outside of the catheter tip as an accumulation undetectable by pressure monitoring or flushing. This platelet material may then be deposited in or swept into a coronary artery (or a brachiocephalic vessel) when the catheter tip nears one of these orifices (Fig. 4).[12,13] In addition, the fine sleeve of platelets which is deposited on the outside surface of a catheter is wiped off this surface by the arterial wall at the

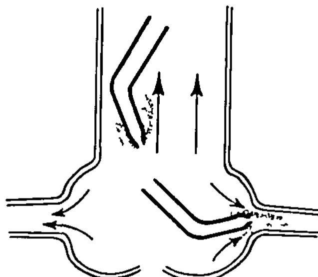


Fig 4 Diagrammatic representation of one mechanism postulated for the propagation of catheter emboli Thrombotic material wiped off guidewire adheres to the outside surface of the tip of the catheter The catheter tip (*upper black heavy lines*) is now in the ascending aorta with the adherent thrombotic material streaming in the direction of blood flow (*vertical arrows*) Embolization from this position can result in a cerebral vascular accident In the lower right the catheter tip is near a coronary arterial orifice Blood flow (*curved arrows*) now causes thrombotic material to stream toward the coronary arteries and to cause coronary embolization even without any injection of contrast material (Reproduced from Takaro et al Acute coronary occlusion following coronary arteriography mechanisms and surgical relief Surgery 72 1018 1972 The C V Mosby Co)

arterial puncture site and accumulates at this site as the catheter is withdrawn (Fig 5*A*, *B* *C* and *D*) There is considerable radiologic evidence to support this hypothesis [20-22] The thrombotic material adheres to the injured arterial wall and if a guide wire has been replaced in the artery in preparation for the introduction of a second catheter, it adheres also to the retained guidewire The tip of the second catheter may sweep this material off the guidewire as it is introduced into the artery In most instances, this material is almost certainly swept away by the blood stream, fragmenting and causing undetectable microscopic peripheral emboli In rare instances it adheres to the tip of the second catheter and causes either cerebral or coronary arterial embolization It appears in the lumen of the coronary vessels as a mass of material consisting of tightly packed coils or cords of aggregated platelets without significant fibrin or red cells [12] We believe that two of the cases reported by Giddings and associates [3] represent emboli of this nature Such an appearance was also noted in two surviving cases in which the embolus was surgically extracted within hours of the coronary arteriographic procedure [12]

Further angiographic evidence to substantiate the possibility of adherence of a sleeve of platelets to a catheter tip is provided by the unusual circumstance of the pocketing of contrast medium in such a sleeve, rendering it radiopaque (Fig 6*A* *B*, and *C*) Less obvious angiographic evidence of the adherence of thrombotic material to a catheter tip is not infrequently noted by the alert angiographer It appears sometimes as a fleck of contrast material adhering to the outside of the catheter, or as a small area of radiolucency in a bolus of contrast medium It is clearly distinguishable from an air bubble by its irregular configuration In one instance the progress of this radiolucent material down a coronary artery and its subsequent lodgment was recorded on an angiogram In this instance it resulted in a non fatal infarction

A third postulated mechanism for the development and propagation of catheter emboli is shown diagrammatically in Fig 7, involving the so called pig tail catheters used for left ventriculography Long, stringy radiopaque thrombotic material adhering to the pigtail catheter was recorded on cineangiography in at least one instance There were no untoward sequelae

In most instances angiographic evidence of coronary embolization consisted of the abrupt appearance during the procedure of total occlusion of a coronary artery shown to be patent only moments before or of stasis or retention of contrast material in a coronary artery after the rest of the material had disappeared (Fig 1) Some of these cases have been assumed to represent subintimal deposition of contrast material, but without pathologic proof [24,25] We have been able to uncover only one pathologically proved case of demonstrable subintimal dissection of the coronary artery during coronary arteriography with deposition of contrast medium in the arterial

wall and conclude that most such appearances represent instead coronary arterial embolization[26]

We believe that the guidewire is an essential element in the pathogenesis of catheter embolism (Figs 4 5 and 7) It is necessary for the transfer of thrombotic material from a foreign body surface (either wire or catheter) to the tip of a cardiac catheter For this reason it is difficult to postulate such a mechanism as occurring using the transbrachial technique with an open brachial arteriotomy and without a guidewire

The probability of increased platelet deposition is increased by prolongation of a study either because of technical difficulty lack of experience or for special studies involving ventricular function or implant or graft opacification It is also increased by stasis of blood flow which would be expected to occur in patients either with hypotension or poor ventricular function and low cardiac output or in vessels involved with atherosclerosis or with both[27,28] Some of the patients in Groups 2 and 3 may also have had coronary emboli from catheters but the resuscitative efforts may have fragmented such emboli so that they were not recognized or pathologic examination may have been incomplete Certainly significant hemodynamic effects[29] as well as serious arrhythmias due to the contrast medium itself[30] or to the irritation of catheters or to reduction of coronary blood flow by catheter tips which partially or completely occlude coronary arterial orifices have been recognized but the relationship between these mechanisms and the deaths in our patients in Groups 2 and 3 must remain conjectural

It is noteworthy that so many patients in this series had diffuse disease in two or three of the major branches of the coronary artery and a substantial proportion had evidence of significant left ventricular dysfunction The highest risk appeared to be in patients with significant stenoses of the left main coronary artery a fact previously noted by Cohen and colleagues[31] They reported a 16 per cent incidence of fatality in association with coronary arteriography in a small group of patients with similar lesions of the left main coronary artery

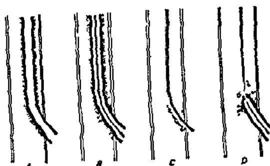


Fig 5 *A* through *D* Diagrammatic representation of another mechanism postulated for the formation and propagation of catheter emboli *A* Catheter (*heavy black lines*) passing through wall of artery (*fine double lines*) and lying in arterial lumen The intra arterial portion of the catheter is covered by a fine deposit of platelets here exaggeratedly thick (*stippled layer*) *B* A guidewire has been inserted into the lumen of the catheter which is now being withdrawn from the artery The layer of platelets is being wiped off the catheter *by the arterial wall* and is accumulating at the arterial puncture site *C* The thrombotic platelet material remains adherent to the puncture site and around the retained guidewire *D* This material is being wiped off the guidewire by the tip of the next catheter inserted into the artery This material adheres now to the tip of this second catheter (Reproduced from Takaro et al Acute coronary occlusion following coronary arteriography mechanisms and surgical relief Surgery 72 1018 1972 The C V Mosby Co)

Hildner and colleagues[32] in a provocative paper entitled Pseudocomplications of cardiac catheterization reported 26 acute events including 12 sudden deaths in patients who were scheduled for cardiac catheterization but did not have the procedure These acute problems included acute myocardial infarctions acute arrhythmias cerebral vascular accidents peripheral arterial occlusion etc strikingly similar types of complications to those which occurred in their catheterized patients following the procedure and also to our series They concluded that one should not presume technical error or operator negligence as the cause of all complications following a cardiac catheterization procedure unless such is demonstrable In any large group of patients it is likely that chance complications will occur as a result of the patient s disease rather than as the result of the procedure This may well have been true for some of the deaths reported

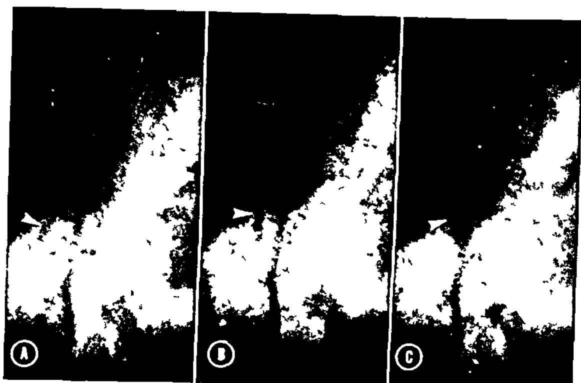


Fig 6 *A* through *C* Sequential frames from cineangiogram showing Judkins type coronary arterial catheter tip in descending thoracic aorta an unusually long sleeve of clot (*arrows*) fortuitously opacified by contrast material is shown clinging to the catheter tip and waving in the blood stream This can easily become an embolus

in our series However, in those cases where an acute coronary occlusion not previously present but demonstrated to have occurred during the angiographic procedure was identified, or a coronary embolus was seen at autopsy an iatrogenic cause for the death must be ascribed

Since our earlier report [12] a number of additional case reports of emergency surgery for acute coronary occlusion or acute myocardial ischemia occurring during coronary arteriography have appeared in the medical literature [26,33,37] Survival was usually reported in patients who were not in cardiogenic shock at the time of surgery There was usually a fatal outcome for those in shock In almost all instances the transfemoral technique had been used Cheng[8] writes that, from his personal conversations with many coronary arteriographers, fatal thromboembolism following selective coronary arteriography is much more frequent than has been generally acknowledged In one of his cases (as well as in one of the series reported by us) the coronary arteries were essentially normal at autopsy—except for the embolic occlusion of a coronary artery

Prevention of fatal complications

Since the incidence of fatal complications as reported here and elsewhere is so much greater following the transfemoral technique, use of the transbrachial technique may prevent some of these deaths If the transfemoral technique is used shortening the procedure minimizing associated studies [3] and avoiding the use of a pigtail type catheter in left ventriculography prior to selective catheterization of the coronary arteries, and the use of non thrombogenic catheters or coatings[38] may be additional safeguards Avoiding the use of a guide wire by using a Teflon sheath to re enter the femoral artery allowing free bleeding between changes of catheters to permit the washing away of withdrawal thrombi at the femoral arterial puncture site or removal of the guidewire and use of the opposite femoral artery for change of catheters or for ventriculography have all been suggested [39] The use of systemic heparin during the procedure has also been advocated[40,41] however while blood clotting due to stasis of blood in catheters may thus be prevented heparin does not alter platelet aggregation nor presumably, platelet deposition on

catheter surfaces [15, 43, 44] Therefore one can not be certain that systemic heparinization will surely prevent acute coronary occlusion from catheter emboli Indeed in one of our patients fatal coronary embolization occurred in spite of the administration of 50 mg of heparin intra arterially It would appear that a combination of heparin plus an agent which would retard platelet aggregation on foreign surfaces would be most effective if the transfemoral technique is used

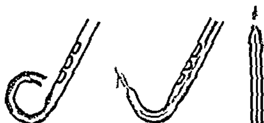


Fig 7 Diagrammatic representation of a third mechanism postulated for the formation and propagation of catheter emboli Platelet thrombus in area of stagnant blood flow in tip of pigtail catheter used for ventriculography may also adhere to the guidewire used for replacing this catheter with a coronary arterial catheter and may be thus transferred to the tip of the second catheter Embolization may occur as noted in Fig 5 (Reproduced from Takaro et al Acute coronary occlusion following coronary arteriography mechanisms and surgical relief Surgery 72 1018 1972 The C V Mosby Co)

Treatment

The surgical treatment of acute coronary occlusion occurring in association with coronary arteriography has been discussed [12] Emergency embolectomy and aortocoronary saphenous vein bypass graft insertion was followed by survival of a number of patients mostly those without cardiogenic shock at the time of the surgery Since emergency surgery may be necessary following coronary arteriography it is probably unwise to perform this procedure regularly in large volumes in a hospital not equipped for emergency cardiac surgery using extracorporeal circulation

Total cost ' of coronary arterial surgery

If the estimate of 35 000 aortocoronary bypass grafts performed since the technique was introduced five years ago is correct as seems likely [11] then it is also very probable that over 100 000 coronary arteriograms have been performed to identify these cases If an estimate of 1 or 2 per cent as the average risk of fatality with coronary arteriography is also correct and this is also quite probable then approximately 1 000 to 2 000 patients have succumbed in association with this diagnostic test. The problem is obviously of some considerable magnitude

Coronary arteriography is undoubtedly an invaluable diagnostic tool which provides morphologic information obtainable in no other way It is worth noting that this information is obtained at some cost however This increases the total mortality rate for which surgery must be held accountable since most of these coronary arteriograms would not have been performed if surgery were not being offered as possible therapy For this reason also fatal complications of coronary arteriography while they probably cannot be completely eliminated must be kept to an absolute minimum

Summary and conclusions

In a Cooperative Study involving 18 hospitals over a four year period the incidence of fatalities occurring in association with coronary arteriography (up to 10 days following the procedure) was 2 1 per cent It was 0 3 per cent using the transbrachial technique and 2 2 per cent using the transfemoral

This disparity is explained by the mechanism of coronary or cerebral arterial embolization from platelet deposits on guide wires and catheters for which evidence is presented in a majority of cases Other mechanisms causing death were acute cardiac arrhythmias acute myocardial infarction complications of the femoral arterial puncture septicemia and unknown causes Patients with significant stenoses of the left main coronary artery were at the greatest risk (6 4 per cent) Prevention of such complications depends upon the technique used speed skill and possibly the use of systemic anticoagulant therapy or antithrombogenic catheters and guide wires

Coronary arteriography should not be undertaken lightly since the risk of a fatal complication at least using the trans

femoral technique, is appreciable This fact is borne out not only by our study, but by reports from a number of other recently reported large series

The risk of coronary arteriography should be reckoned as part of the 'total cost' of coronary arterial surgery

Arteriography logs and/or cases were contributed for this study by the following VA Hospitals Ann Arbor Brooklyn Buffalo Dallas Hines Lexington Little Rock Long Beach Los Angeles Madison Minneapolis Oteen Palo Alto Salt Lake City San Francisco Seattle and Washington and also by Loyola University Hospital The cooperation of the cardiologists surgeons angiographers and pathologists at these Hospitals is gratefully acknowledged We are also very grateful to R L Crislip M D of Portland Oregon who loaned the films from which Fig 6 was taken

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Left ventricular gallop sound and acute myocardial infarction

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Pulmonary râles, a ventricular gallop sound (VGS), and cardiogenic shock have important prognostic implications in patients with acute myocardial infarction. The classification of patients with acute myocardial infarction into four groups on the basis of these bedside findings, as proposed by Killip and Kimball[1] has proved to be quite useful in predicting immediate survival. Class IV patients, those with severe left ventricular power failure, have an extremely poor prognosis. Intensive studies are now being made of the possible benefits of volume expansion,[2] circulatory assistance,[3,4] or vein bypass surgery[5-7] during the acute phase in these patients. The purpose of this study was to correlate a ventricular gallop sound heard in patients with acute myocardial infarction at the time of admission to the Coronary Care Unit *with survival during the acute phase*. The clinical objective was to identify a group of patients who might benefit from more intensive therapeutic efforts.

Methods

During a 24 month period, 156 patients with proved myocardial infarction were admitted to the Myocardial Infarction Research Unit at the University of Alabama in Birmingham. Criteria for diagnosis included a compatible clinical history with the development of diagnostic Q waves or evolution of ST segment and T wave abnormalities and characteristic changes in SGOT and LDH activity in serial blood samples. Patients with acute myocardial infarction were divided into three groups on the basis of their initial electrocardiogram.[8,9] Anterior myocardial infarction included patients with electrocardiographic evidence of either acute anteroseptal or anterolateral infarction. Inferior myocardial infarction included patients with either diaphragmatic or posterior QRS changes. Patients in the third group with ST changes only were felt to have had definite myocardial necrosis on clinical grounds *with a typical rise and fall in serum enzymes (SGOT and/or LDH)*, but without electrocardiographic evidence of transmural infarction. Patients who presented with left bundle branch block or a nonspecific intraventricular conduction defect were included in this last group as well as patients with subendocardial infarction (myocardial necrosis).

Patients were classified on bedside exami-

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nation according to the myocardial infarc tion classification of Killip and Kimball[1] An uncomplicated patient (Class I) had neither pulmonary rales nor a ventricular filling gallop sound Patients with mild or moderate congestive heart failure (Class II) exhibited basilar pulmonary rales persistent after coughing and/or a ven tricular filling gallop sound detected by at least one of the investigators Pulmonary edema (Class III) was defined as the pres ence of moist rales over more than half of the lung fields Shock associated with myocardial infarction (Class IV) was diag nosed clinically when there was evidence of severely decreased peripheral perfusion such as cool clammy skin weak pulse mental obtundation or oliguria and a sys tolic blood pressure below 90 mm Hg or 80 mm Hg below previous blood pressure

A ventricular gallop sound was consid ered present if it was audible by at least two observers on the day of admission to the Coronary Care Unit Phonocardiograms were not recorded on these patients and therefore the presence or absence of a ventricular gallop sound is based on clinical observations The accuracy of the senior authors in the recognition of a ventricular gallop sound has been confirmed by com parison to phonocardiography in previous studies[10]

Pulmonary artery pressure was measured in 49 patients admitted with acute myo cardial infarction In 4 additional patients a catheter was introduced into the brachial artery and advanced to the left ventricle for measurement of left ventricular end diastolic pressure After explanation of the procedure to the patient and/or relatives informed consent was obtained Cardiac catheterization was performed primarily in patients with clinical heart failure and/or shock and the detection of a VGS alone or with pulmonary rales was considered clinical evidence of heart failure The pa tient remained in a radiolucent bed and a ceiling mounted fluoroscope was used dur ing catheter manipulation Under sterile conditions and local anesthesia a cutdown was made on an antecubital vein Early in the investigation standard radiopaque car diac catheters were used but later were replaced by Swan Ganz catheters In the right atrium 50 mg of lidocaine was in jected and the catheter was advanced to the

Table I Ventricular gallop sound (VGS) in relationship to infarct location and mortality rate

		Survived	Died	Total
VGS present	ANT	22	16	38
	INF	7	2	9
	ST	9	7	16
VGS absent	ANT	31	8	39
	INF	31	4	35
	ST	17	2	19
		117	39	156

Abb at ns ANT = anterior myocardial infarction INF = af nor myocardial infarctio ST = myocardial necr sis

pulmonary artery The mid position of the anteroposterior chest thickness was used as reference for the level of the right atrium

A chi square test of independence was performed for each of the variables shown in the tables comparing mortality rate with the presence or absence of a ventricular gallop sound A t test was performed to de termine the significance of different mean left ventricular filling pressure in patients with or without ventricular gallop sounds

Results

A ventricular gallop sound was audible in 63 of 156 patients (40 per cent) at the time of admission to the Coronary Care Unit (Table I)

The pulmonary artery or left ventricular end-diastolic pressure was measured in 53 patients with acute myocardial infarction (Fig 1) In 27 patients a VGS was audible and in 26 the sound was not detected The time delay from admission to the Unit and measurement of pulmonary artery pressure ranged from 1 to 84 hours but 42 patients (79 per cent) were studied within 24 hours There was no significant difference in delay of study in patients with a VGS (13 5 ± 20 7 hours) or those without the finding (18 6 ± 19 1 hours) In the 26 patients with out a VGS the pulmonary artery end diastolic pressure (PAEDP) or left ven tricular end diastolic pressure (LVEDP) ranged from 2 to 44 mm Hg and was less than 12 mm Hg in 11 patients In the 27 patients with a VGS 25 revealed a PAEDP or LVEDP > 12 mm Hg and 2 possessed a PAEDP within the normal range 7 and

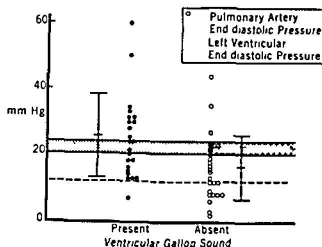


Fig 1 Ventricular gallop sound and left ventricular filling pressure in acute myocardial infarction (dashed line = 12 mm Hg shaded bar = 20 to 24 mm Hg) Twenty five of 27 patients with a VGS demonstrated abnormal elevations of PAEDP or LVEDP whereas 11 of 26 patients without a VGS revealed normal left ventricular filling pressure Patients with a VSG and PALDP or LVEDP < 20 mm Hg could have received a volume expander for improvement of left ventricular function and patients with a VGS and PAEDP or LVEDP > 24 mm Hg would be candidates for blood volume reduction for optimal ventricular performance

11 mm Hg respectively In the 25 patients with a VGS and an abnormally elevated PAEDP or LVEDP above 12 mm Hg 8 patients revealed PAEDP or LVEDP < 20 mm Hg and 13 patients demonstrated a PAEDP or LVEDP > 24 mm Hg An audible VGS in patients with acute myocardial infarction was associated with an abnormally elevated PAEDP or LVEDP in 25 of 27 patients Mean left ventricular filling pressure was higher in those with a VGS (25 1 ± 12 6) than in those without a VGS (16 3 ± 9 65) (P < 005)

In hospital deaths occurred in 40 per cent of patients with a ventricular gallop sound, as opposed to 15 per cent of patients without a ventricular gallop sound (P < 001) A ventricular gallop sound was present in 14 of 20 patients (70 per cent) with cardiogenic shock (Table II) Four of six patients (67 per cent) in cardiogenic shock without a ventricular gallop sound and 11 of 14 (79 per cent) with this physical finding died in the hospital (P > 05) Although a left ventricular gallop sound was associated with an increased risk of death in the total group of patients studied, this physical finding was not significantly associated with death from cardiogenic shock

A twofold increase in mortality rate was noted in patients with anterior myocardial infarction and a ventricular gallop sound (P < 05) A fourfold increase in mortality rate was noted *in patients with ST changes* only—i e , myocardial necrosis, and a ventricular gallop sound (P < 05) (Table I) Of the seven patients who died with myocardial necrosis and a ventricular gallop sound, only three died in cardiogenic shock A ventricular gallop sound was heard on admission in 11 of 15 patients who subsequently died with left ventricular power failure Therefore, a left ventricular gallop sound present on admission to the hospital was not useful in predicting which patients would subsequently die in cardiogenic shock

The presence of a ventricular gallop sound in patients with anterior and ST segment infarctions was associated with an *unfavorable prognosis for survival There* was no significant association between a ventricular gallop sound and death due to cardiogenic shock (P > 05) The increased risk of death in patients with anterior or ST segment infarction is largely attributable to deaths due to causes other than cardiogenic shock Only patients with inferior infarction seemed to be at increased risk of death from cardiogenic shock in the presence of a ventricular gallop sound However the number of patients with inferior infarction was too small for these results to be statistically significant

Discussion

Although ventricular gallop sounds are useful in the clinical recognition of heart failure the prognostic importance of this auscultatory finding has not been delineated in patients with acute myocardial infarction Thus while a ventricular gallop sound may be associated with an over all increase in mortality rate in patients with acute myocardial infarction this finding does not have high predictive value for death in the individual patient It is important to note that patients having ST segment changes only—i e myocardial necrosis, in association with a ventricular gallop sound have an increased hospital mortality rate Thus increased alertness for arrhythmias or depressed left ventricular function must be maintained in this group of patients who are otherwise generally considered to have an uncomplicated clinical course

A left ventricular diastolic gallop sound is well recognized as a clinical hallmark of left ventricular failure The genesis of this sound remains obscure but is generally felt to represent an imbalance between the volume of left ventricular inflow during the rapid filling phase of diastole and the ability of the left ventricle to accommodate the amount of inflow [11 12] This sound may result from sudden tension upon the mitral valve apparatus as the ventricle rapidly expands and elongates [13]

Porter and colleagues[10] have shown that left ventricular wall stress values at peak left ventricular filling rates in patients with chronic valvular heart disease and a ventricular gallop sound may be normal This supports the concept of a relatively compliant left ventricle in this group of patients although direct measurements of left ventricular compliance remain under investigation [14] One patient in Porter s series however with acute mitral regurgitation and left ventricular failure had a very high wall stress during peak left ventricular filling This would suggest a relatively non-compliant left ventricle and perhaps a different mechanism for the ventricular gallop sound These investigators also found that patients with primary myocardial disease and a ventricular gallop sound had elevated wall stress values during peak LV filling An abnormal elevation in wall stress during this phase of diastole would indicate a non compliant left ventricle and thus another mechanism for the ventricular gallop sound than in those patients with relatively compliant left ventricles during early diastole The frequent occurrence of atrial gallop sounds in patients with acute myocardial infarction is taken as evidence for reduced left ventricular compliance [14] However the hemodynamics of atrial gallops in acute infarction remain to be delineated and many of these patients also have ventricular gallop sounds

In the present investigation 25 of the 27 patients with a VGS demonstrated an abnormal PAEDP or LVEDP greater than 12 mm Hg Ratshin and associates[15] have previously reported in patients developing shock with acute myocardial infarction that a VGS was always associated with a left ventricular or pulmonary artery end diastolic pressure greater than 12 mm Hg

Table II Ventricular gallop sound (VGS) and mortality rate in patients with cardiogenic shock (n = 20)

	Survived	Died	Total
VGS present	3	11	14
VGS absent	2	4	6
Total	5	15	20

Russell and co workers[17] have demonstrated that in patients with acute infarction left ventricular filling pressure can be elevated with blood volume expansion and ventricular performance can be improved In Russell s studies optimal improvement in left ventricular function occurred with LVEDP or PAEDP in a range of 20 to 24 mm Hg In the present study in the 25 patients with a VGS and PAEDP or LVEDP > 12 mm Hg 8 patients revealed PAEDP or LVEDP < 20 mm Hg and 13 patients exhibited a PAEDP or LVEDP > 24 mm Hg The patients with a VGS and PAEDP or LVEDP < 20 mm Hg could have received a volume expander in order to improve left ventricular function and the patients with a VGS and PAEDP or LVEDP > 24 mm Hg would be candidates for blood volume reduction for optimal ventricular performance Additional pharmacologic observations emphasize the need for accurately assessing left ventricular function in acute myocardial infarction Several recent clinical studies have failed to demonstrate significant hemodynamic improvement following digitalis administration in acute myocardial infarction [18 20] Experimental and clinical investigations have shown an increased sensitivity to digitalis with toxic arrhythmias during the immediate post infarction period [21 22] Therefore a patient with acute myocardial infarction and a VGS should be suspected of having depressed left ventricular function which could be improved with volume expansion or reduction However measurement of pulmonary artery pressure is necessary to identify these patients and to select the appropriate agents for improving left ventricular function The present investigation confirms the need for hemodynamic monitoring in patients with a VGS in the presence of mild or severe heart

failure as well as in cardiogenic shock. The best treatment for such patients should be based on initial and continuous measurements of left ventricular hemodynamics.

Summary

A ventricular gallop sound, pulmonary râles, and cardiogenic shock have important prognostic implications in patients with acute myocardial infarction. The purpose of this study was to examine the relationship between VGS and death in myocardial infarction. A VGS was audible in 63 of 156 patients (40 per cent) with proved myocardial infarction admitted to a Myocardial Infarction Research Unit during a 24 month period. Fifty three patients were studied hemodynamically and 25 of 27 patients with an S_3 gallop demonstrated an abnormally elevated pulmonary artery end diastolic pressure greater than 12 mm. Hg. Hospital deaths occurred in 40 per cent of patients with a VGS versus 15 per cent of those without this auscultatory finding. Seventy five per cent of patients in cardiogenic shock died but a VGS was not significantly associated with death in this group. Although in all patients a VGS was associated with increased mortality rate, deaths were not due to cardiogenic shock. This study confirms the need for hemodynamic monitoring in patients with acute myocardial infarction who exhibit a VGS as evidence of left ventricular power failure. Treatment should be based upon both clinical observations and continued evaluation of the hemodynamic alterations associated with left ventricular power failure.

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Coronary arteriographic findings in patients with axis shifts or S-T-segment elevations on exercise stress testing

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When transient myocardial ischemia occurs either in spontaneous attacks of angina pectoris or induced by an imposed stress such as exercise or hypoxia, it has been long known that there may be electrocardiographic changes expressed mainly as shifts in the S-T segment. The usual "positive response" is a depression in the S-T segment in the standard and/or precordial leads.

The description and extent of shift couched in the term "depression of the S-T segment" has been the subject of many papers with focus on its specificity and discriminatory power in the identification of inadequate coronary perfusion and coronary disease. Data concerning the use of exercise tests are voluminous and in the United States one of the most popular exercise tests has been that devised by Masters and others and much information concerning its diagnostic and prognostic value is available.[1,2] One of us (Burchell[4]) has reviewed the usefulness of the exercise test in the different approaches of clinician, epidemiologist, and work physiologist.

The S-T-segment shift related to ischemia when it occurs is usually perpendicular to the long axis of the heart so that one may conceive of a shell of ischemic myocardium presumably proximate to the endocardium, which is relatively more ischemic than that proximate to the epicardium, thus creating a mean injury dipole expressed as an S-T-segment depression in the standard leads and elevation in the right arm unipolar lead, and depression of the left precordial leads. Modifications of the latter leads (e.g., right shoulder to apical area) are commonly used while monitoring the electrocardiographic response during exercise. It has been long noted that occasionally the electrocardiographic response to induced stress could be manifested by S-T-segment elevation in the precordial leads or in leads subtending posterior inferior wall of the heart resulting in an electrocardiogram (ECG) simulating acute infarction. Such patterns have also been seen in individuals having spontaneous angina, particularly those variants characterized by prolonged pain at rest, a phenomenon in patients emphasized as distinctive by Prinzmetal and

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Table I Electrocardiographic (resting and postexercise) and coronary angiographic findings in sub

Patient	Age	Sex	Resting ECG			S T–segment elevation (mm)									
			Normal or minimal ST T	AMI	DMI	I	II	III	aV_R	aV_L	aV_F	V_1	V_2	V_3	V_4
E A	47	M	✓					2			1				
B S	42	M	✓					0 5			1				
G B	49	M	✓				0 5	1			1 5				
K C	44	M	✓									1			
A F	62	M	✓									1	2	2	2
V K	62	M	✓									3	3	3	
G L	60	M	✓									1 5	2 5	4	1
M W	66	F	✓									1 5	2	1 5	
M M	37	M	✓									1 5			
L B	44	M		✓											2 5
R K	38	M		✓								1	2	2	2
L N	49	M		✓								1 5	2	3	
A P	50	M		✓									2	2	
J F	37	M			✓			0 5			0 5				
C M	56	M			✓							2	5		
P B	45	M		✓	✓		0 5	1			1				
H N	60	M		✓	✓							2 5	1 5	2	
C S	38	M		✓	✓		0 5	1			0 5	1 5	1 5	2 5	3 5

C A. obstruc = coronary artery obstruction Rt = right LAD = left anterior descending LC = left circumflex

associates[5] and Silverman and Flamm[6] The reasons underlying this effect have been conjectural but obviously it suggested an obstructive lesion localized predominantly to one of the major coronary branches With the availability of coronary arteriograms one has been allowed to make correlations between this unusual S T–segment shift and the locus of the coronary obstruction and this was the basic objective of this study A similar study has been reported by Fortuin and Friesinger[7]

In some instances exercise may produce aberration in the pattern of excitation of the left ventricle, including complete left bundle branch block There may also be more subtle changes which one can attribute to disturbances in excitation pathways in the proximal or distal portions of the left bundle fasciculis These alterations are expressed primarily in the change in axis deviation in the frontal plane, and an attempt has been made in this study to relate these changes when they occurred to the pattern of coronary arterial obstruction

Materials and methods

This study was based on a retrospective review of the findings in 158 patients who had both treadmill tests and coronary arteriograms at the University of Minnesota Hospitals prior to Sept 1 1971 The purpose of the study was to evaluate the association between coronary arteriographic findings and exercise induced S T–segment elevations or axis shifts on maximal treadmill exercise tests

The treadmill tests done in all 158 patients were multistage, maximal exercise tolerance tests according to Doan and co workers[8] in which the ECG was monitored by a single bipolar lead during exercise and by a full 12 lead ECG which was recorded in the supine position on a multichannel machine immediately before and after exercise and at frequent intervals thereafter All patients who were found to have impressive exercise induced S T–segment elevations or impressive exercise induced left or right axis shifts were included in the study In the patients with exercise induced S T–segment elevations the height and ECG location of the eleva

-with postexercise ST segment elevation

		%C A obstruc			Collaterals
V_5	V_6	Rt	LAD	LC	
		95	40	60	To right
		99	90	100	LAD to LC
		90	0	0	None
		0	85	0	None
		25	100	0	Rt to LAD
		50	100	90	None
		50	95	75	None
		50	95	0	Rt to LAD
		0	0	0	None
		0	50	0	None
		100	100	45	Rt to LAD
		0	100	0	Minimal
		100	100	25	Rt to LAD
		90	90	90	None
		100	100	100	To all 3
		100	100	100	To all 3
		100	95	95	To Rt
2		100	100		To Rt to LAD

tions were tabulated along with the coronary arteriographic findings In the patients with exercise induced axis shifts the magnitude of the shift was determined on the hexaxial reference system by using the QRS magnitude before and after exercise in Leads I and III and in Leads I and aV_F The direction and magnitude of the axis shifts were tabulated along with the coronary arteriographic findings

The coronary arteriograms of 154 of the 158 patients had already been reviewed as part of a larger continuing study In all 154 patients the degree of obstruction of the right left anterior descending and left circumflex coronary arteries had been graded on a scale of 0 to 4 with 0 being no obstruction 1 standing for 1 to 24 per cent obstruction 2 equaling 25 to 49 per cent obstruction 3 being 50 to 99 per cent obstruction and 4 complete obstruction The presence and the extent of collateral circulation was also recorded in each patient This system for grading coronary artery obstruction was used in the tabulation of the location and severity of the coronary artery disease in the groups of patients with exercise induced axis shifts However in the group of patients with exercise induced S T-segment elevations there was an additional review of the coronary arteriographic findings and an estimate of the actual percentage, rather than grade of coronary artery obstruction was included in the tabulation of the location and severity of the coronary artery disease

Results

Exercise induced S T-segment elevations Exercise induced S T-segment elevations which were impressive to us were found in 18 of the 158 patients studied (Table I) These S T-segment elevations were present in the precordial leads only in 12 patients (Fig 1) in the inferior limb leads only in 5 patients (Fig 2) and in both the precordial and the inferior limb leads in one patient The S T-segment elevations ranged from 1 to 5 mm in the precordial leads and from 0 5 to 2 mm in the inferior limb leads (standardization 1 cm = 1 mv) In 9 of the 18 patients there was no evidence of a previous myocardial infarction on the resting ECG But of the remaining 9 patients 4 had ECG evidence of a previous anterior infarction 2 had ECG evidence of a previous inferior infarction and 3 had ECC evidence of both a previous anterior and inferior infarction (Table I)

When the coronary arteriograms of the 13 patients with exercise induced precordial S T-segment elevations were reviewed it was found that there was at least an 85 per cent obstruction of the left anterior descending artery in 11 of the 13 patients (Table II) In addition in a twelfth patient there was 50 per cent diffuse obstruction of the left anterior descending artery along with normal right and left circumflex arteries and evidence of a previous anterior myocardial infarction on the resting ECG

Of the six patients with precordial S T-segment elevations and no evidence of a myocardial infarction on resting ECG five had at least an 85 per cent obstruction of the left anterior descending artery but none had severe obstruction of the right coronary artery The sixth patient in this group had normal coronary arteriograms and the least impressive S T-segment elevations of all the patients studied In this

patient, there was an S T–segment elevation of 1 5 mm, which was present only in Lead V_1 and which was associated with reversal of the T wave direction from inverted to upright (Fig 3)

Of the 7 patients with precordial S T–segment elevations and evidence of a previous myocardial infarction on the resting ECG 6 had at least an 85 per cent obstruction of the left anterior descending artery, and the seventh had a 50 per cent diffuse obstruction as discussed above But in 5 of these 7 patients there was also severe generalized disease with an 85 per cent obstruction of the right coronary artery as well as the left

When the coronary arteriograms of the 6 patients with exercise induced inferior limb lead S T–segment elevations were reviewed, it was found that there was at least an 85 per cent obstruction of the right coronary artery in all 6 patients (Table III) This severe obstruction was present only in the right coronary artery in 2 of the 3 patients with no evidence of a previous myocardial infarction on the resting ECG But there was at least an 85 per cent obstruction in all 3 of the major coronary arteries in each of the 3 patients with evidence of a previous myocardial infarction on the resting ECG

In 16 of the 18 patients with localized exercise induced S T–segment elevations these changes were associated with at least an 85 per cent obstruction of the compatible coronary artery In a seventeenth patient they were associated with a 50 per cent diffuse obstruction of the compatible coronary artery and no obstruction of the other two major vessels Hence there was severe obstruction of the compatible coronary artery in 17 of the 18 patients with exercise induced S T–segment elevations And as discussed previously the only patient who did not have severe obstruction of the compatible vessel also had the least impressive exercise induced S T–segment elevations in the entire group

The severe obstruction of the coronary artery compatible with anterior or inferior ischemic localization was accompanied by varying degrees of obstruction of the other major coronary arteries In those patients with no evidence for a previous myocardial infarction on the resting ECG severe obstruction was often present only in the compatible coronary artery This was the case in 7 of the 9 patients who had no previous infarction on the ECG But in those patients who had evidence of a previous myocardial infarction on the resting ECG, severe obstruction of the compatible coronary artery often co existed with severe obstruction of the other major coronary arteries as well This was the case in 7 of the 9 patients who had a previous infarction on the ECG

Exercise induced axis shifts Exercise induced axis shifts were noted on visual inspection in 13 of the 158 patients studied In 9 of the patients there was an exercise induced right axis shift (Fig 4) and in 4 of the patients there was an exercise induced left axis shift (Fig 5) In the 9 patients with an exercise induced right axis shift the change in axis with exercise ranged from a change of as little as +14 degrees to a change of as much as +91 degrees (Table IV) In the 4 patients with an exercise induced left axis shift the change in axis after exercise ranged from a change of as little as −11 degrees to a change of as much as −56 degrees (Table V) In addition there was a slight prolongation of the QRS complex after exercise in 2 of the 4 patients with exercise induced left axis shifts

A tabulation of the coronary arteriographic findings in the 9 patients with exercise induced right axis shifts did not demonstrate any tendency toward predominant localization of coronary artery obstruction in any particular vessel (Table IV) Also as the magnitude of the exercise induced right axis shift increased there was no consistent increase in the severity of the coronary artery obstruction found on arteriography (Table IV) And furthermore the coronary artery obstruction found in these 9 patients was if anything less severe than that found in the total group of patients analyzed Only 4 of the 9 patients with exercise induced right axis shifts had a 50 per cent or more obstruction of at least one major coronary artery as compared to 103 of the total group of 154 patients analyzed (Table VI)

A tabulation of the coronary arteriographic findings in the 4 patients with exercise induced left axis shifts id demon

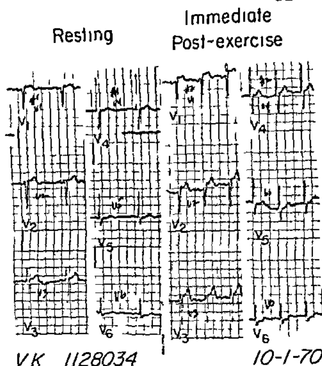


Fig 1 Pre and postexercise ECG s of V K (precordial leads only) showing transient exercise-induced S-T-segment elevations in Leads V_1 to V_3

Table II Frequency of at least 85 per cent obstruction in patients with exercise induced precordial S T elevation

	Resting ECG				
	No infarct	*Anterior infarction*	*Inferior infarction*	*Anterior and inferior infarction*	*Total*
Number of patients	6	4	1	2	13
Right coronary	0	2	1	2	5
Left anterior descending	5	3	1	2	11
Left circumflex	1	0	1	2	4

An additional patient in this group had 50 per cent obstruction of the left anterior descending artery with normal right and left circumflex arteries.

strate a tendency toward localized coronary artery obstruction (Table V) It was found that 3 of these 4 patients had severe coronary artery disease with complete obstruction of the left anterior descending artery However the number of patients in this group was too small for a satisfactory comparison with the larger group (Table VI)

Discussion

Exercise induced S T-segment elevations Reversible nonexercise induced S T-segment elevations in leads subtending the epicardial surface have previously been reported in association with severe coronary artery disease In their review of the subject Fortuin and Friesinger[7] cited the

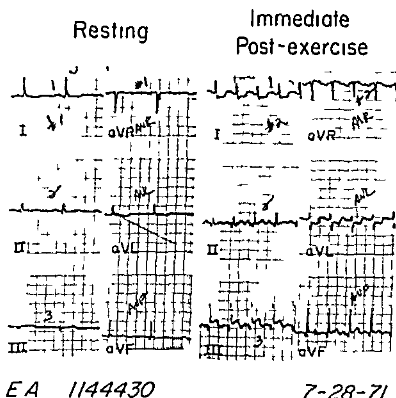


Fig. 2. Pre- and postexercise ECG's of E. A. (extremity leads only) showing transient exercise-induced S-T-segment elevations in Leads III and aVF.

Table III. Frequency of at least 85 per cent obstruction in patients with exercise-induced inferior S-T elevation

	Resting ECG				
	No infarction	*Inferior infarction*	*Anterior infarction*	*Anterior and inferior infarction*	*Total*
Number of patients	3	1	0	2	6
Right coronary	3	1	0	2	6
Left anterior descending	1	1	0	2	4
Left circumflex	1	1	0	2	4

results of various animal experiments as supporting evidence for the importance of this association. They noted that temporary ligation of a coronary artery has been shown to produce reversible S-T-segment elevations in dogs[9] and that these changes usually do not occur unless the blood flow is reduced by at least 70 per cent.[10] They also noted that in that variant of angina pectoris particularly emphasized by Prinzmetal and colleagues[3] reversible S-T-segment elevations are associated with severe coronary artery disease on coronary arteriographic or postmortem examinations.

Reversible S-T-segment elevations on exercise ECG's have been reported in association with severe localized coronary artery disease and also in association with ventricular aneurysms. Fortuin and Friesinger reported total or near total obstruction of the compatible coronary artery in 11 of 12 patients with localized exercise-induced S-T-segment elevations. It is note

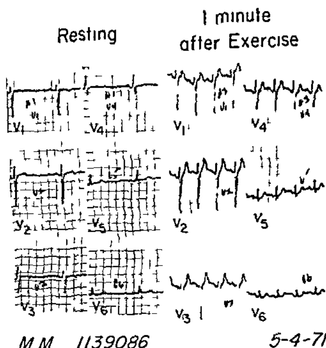


Fig 3 Pre and postexercise ECG s of M M (precordial leads only) showing transient exercise induced S-T-segment elevations in Lead V_1 in association with reversal of the T wave direction from inverted to upright

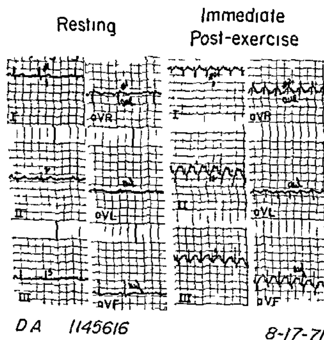


Fig 4 Pre- and postexercise ECG s of D A (extremity leads only) showing a transient exercise induced right axis shift.

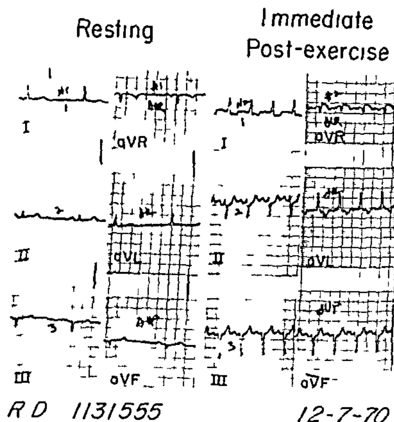


Fig 5 Pre and postexercise ECG s of R D (extremity leads only) showing a transient exercise-induced left axis shift

worthy that only one of these 12 patients had a history consistent with Prinzmetal s variant of angina pectoris Gorlin and associates[11] reported S T–segment elevations in 16 of 24 patients with ventricular aneurysms, and in 4 of the 16 patients with S T–segment elevations these changes were noted only after a Master s two step test Rubenstein and co workers[12] reported abnormal left ventriculograms in 8 of 11 patients with S T–segment elevations on exercise ECG s Localized left ventricular dysfunction was found in 8 of the 9 patients with a previous myocardial infarction but this finding was not present in the 2 patients without a previous infarction

In the University of Minnesota series exercise induced S T–segment elevations were associated with severe obstruction of the coronary artery compatible with the localization of the ischemic zone in 17 of the 18 patients studied Furthermore the severe obstruction was limited to the compatible coronary artery in 7 of the 9 patients without a previous infarction seen on the ECG, but it was present in both the compatible coronary artery and in other major coronary arteries as well in 7 of the 9 patients with a previous infarction on ECG Hence it appears that severe coronary artery disease is likely to be limited to the compatible coronary artery in patients without a previous infarction on the ECG But it appears that severe coronary artery disease is likely to be present in multiple coronary arteries including the compatible coronary artery, in patients with a previous infarction on ECG The presence of collaterals connecting with the most diseased artery ("compatible coronary artery) did not seem to alter the exercise induced S T–segment elevation

Exercise induced axis shifts Acute transient right and left axis shifts have previously been reported after the injection of radiopaque dye during coronary arteriography [13] after acute myocardial infarction [14] and after exercise tolerance testing [15,16] Both right and left exercise induced axis shifts have been reported in patients presumed to be free of coronary artery disease[15] and in patients known to have angina pectoris [16]

Table IV Grade of coronary artery obstruction in patients with exercise induced right axis shift

Patient	Resting ECG	Treadmill test	Axis shift (degrees)	Axis (degrees)		C A obstruc				Collateral	Postexercise QRS prolongation
				Pre exercise	Post-exercise	Rt	LM	LAD	LC		
F T	ST T changes	+	+14	+41 to	+55	0	0	0	0	–	–
J A	Normal	–	+22	+61 to	+83	0	0	0	0	–	–
F S	LVH ST T changes	+	+25	+16 to	+41	4	2	3	4	+	–
R J	?LVH ST T changes	+	+38	+47 to	+85	0	0	3	1	–	–
R E	ST T changes	+	+39	+55 to	+94	0	0	1	0	–	–
H H	Normal	+	+59	+19 to	+78	2	0	1	1	–	–
W E	Normal	+	+68	+37 to	+105	3	3	3	3	–	–
D A	Normal	–	+79	+62 to	+141	0	0	0	0	–	–
B S	Normal	+	+91	+22 to	+113	3	0	3	1	+	–

C A obstruc = coronary artery obstruction Rt = right LM = left main LAD = left anterior descending LC = left circumflex LVH = left ventricular hypertrophy
*0 = None 1 = 1 to 24 per cent 2 = 25 to 49 per cent 3 = 50 to 99 per cent 4 = complete obstruction.

Table V Grade of coronary artery obstruction in patients with exercise induced left axis shift

Patient	Resting ECG	Treadmill test	Axis shift (degrees)	Axis (degrees)		C A obstruc				Collateral	Postexercise QRS prolongation
				Pre exercise	Post exercise	Rt	LM	LAD	LC		
L N	ASMI	+	−11	−36 to	−47	0	1	4	0	+	+
V C	Normal	–	−31	−23 to	−54	0	0	0	0	0	–
R D	ST T changes	+	−36	−9 to	−45	3	0	4	4	+	+
V K	ST T changes	+	−56	+40 to	−16	2	0	4	3	+	–

C A obstruc = coronary artery obstruction Rt = right LM = left main LAD = left anterior descending LC = left circumflex ASMI = anteroseptal myocardial infarct
*0 = None 1 = 1 to 24 per cent 2 = 25 to 49 per cent 3 = 50 to 99 per cent 4 = complete obstruction.

Several aspects of the trifascicular nature of the ventricular conduction system suggest the possibility that exercise induced left axis shifts may be associated with obstructive disease of the left anterior descending artery First the blood supply to the left anterior fasciculus as described by Rosenbaum and associates[17] is derived entirely from the left anterior descending artery However it is not clear if this arrangement persists in a diseased heart with multiple collateral vessels[18] Second in Rosenbaum s series the most common cause of left anterior fasciculus block was thought to be coronary artery disease And third transient left anterior fasciculus block is sometimes found in association with an acute anteroseptal myocardial infarction

Of the 4 patients in the Minnesota series who developed exercise induced left axis shifts 3 developed a shift beyond −45 degrees consistent with a complete left anterior fasciculus block and the fourth developed a shift to −16 degrees consistent with a partial left anterior fasciculus block The finding that 3 of the 4 patients in this group did have complete obstruction of

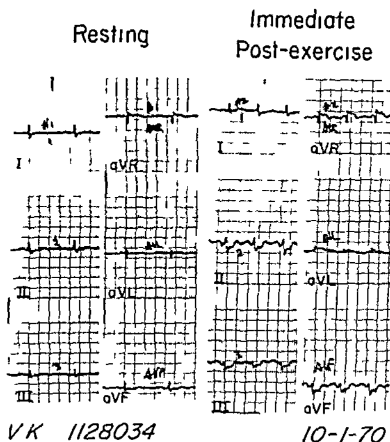


Fig. 6. Pre- and postexercise ECG's of V. K. (extremity leads only) showing a transient exercise-induced left axis shift prior to coronary artery surgery.

the left anterior descending artery is very suggestive of a causal relationship. However, the fourth patient in this group had normal coronary arteriograms. And since there were only 4 patients in the entire group, it was not possible to make a satisfactory comparison to the total group of patients analyzed. Hence the significance of the apparent association between exercise-induced left axis shifts and severe obstruction of the left anterior descending artery remains unclear.

It also seems possible that exercise-induced right axis shifts could be associated with obstructive disease of the right and left coronary arteries. However, on the basis of Rosenbaum's work it would seem that such an association would be found less frequently with right axis shifts than with left axis shifts. First, the blood supply to the left posterior fasciculus is derived from both the left and the right coronary arteries. Second, the left posterior fasciculus is both shorter and thicker than the left anterior fasciculus. Third, left posterior fasciculus blocks occur with a much lower

Table VI. Frequency of at least 50 per cent obstruction in patients with exercise-induced axis shift

	No. of patients	*Less than 50% obstruction*	*At least 50% obstruction*
Left axis shift	4	1	3
Right axis shift	9	5	4
All patients analyzed	154	51	103

frequency than left anterior fasciculus block.

Of the 9 patients in this series who developed *exercise-induced* right axis shifts only one developed a *shift beyond* +120 degrees and only 3 developed shifts beyond +100 degrees. Thus the postexercise axis approached Rosenbaum's criteria of about +120 degrees for complete left posterior fasciculus block in only 3 of the 9 patients. There was no consistent association between the localization of severity

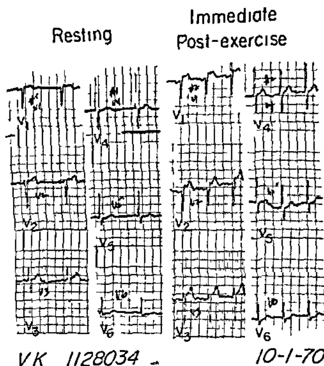


Fig 7 Pre and postexercise ECG s of V K (precordial leads only) showing transient S-T-segment elevations in Leads V_1 to V_4 prior to coronary artery surgery

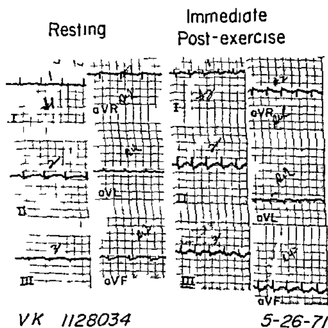


Fig 8 Pre- and postexercise ECG s of V K (extremity leads only) showing a reversal of the preoperative exercise-induced left axis shift after a successful surgical bypass of an obstructing lesion in the left anterior descending artery

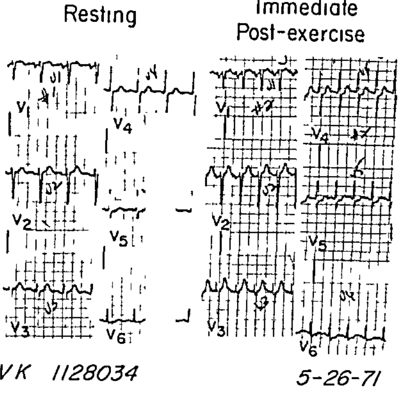


Fig 9 Pre and postexercise ECG s of V K (precordial leads only) showing a marked reduction of the preoperative exercise induced S-T-segment elevations after a successful surgical bypass of an obstructing lesion in the left anterior descending artery

of obstructive coronary artery disease and the magnitude of the exercise induced right axis shifts Furthermore severe coronary artery disease with greater than 50 per cent obstruction of any major vessel was present in only 4 of the 9 patients with exercise induced right axis shifts And finally there was no coronary artery obstruction in the only patient whose axis shifted beyond +120 degrees with exercise Hence it is concluded that there is no predictable association between exercise induced right axis shifts and the likelihood of finding severe obstruction of a major vessel on coronary arteriography

Case report

The behavior of the exercise induced ECG changes after successful coronary artery bypass surgery was of particular interest in the case of V K When initially studied he was able to tolerate only 2 minutes and 18 seconds of exercise on the treadmill and the ECG showed an exercise induced left axis shift from +40 degrees to −16 degrees (Fig 6) and exercise induced S T-segment elevations of 3 mm in Leads V_1 to V_4 (Fig 7) On arteriography these changes were found to be associated with 100 per cent obstruction of the left anterior descending artery 90 per cent obstruction of the left circumflex artery and 50 per cent obstruction of the right coronary artery Several months later after coronary artery bypass surgery the patient was restudied This time he was able to tolerate 4 minutes and 35 seconds of exercise on the treadmill But the ECG now showed an exercise induced right rather than left axis shift (Fig 8) and only 0 5 mm S-T-segment elevations in Leads V_1 to V_3 (Fig 9) On arteriography these changes were found to be associated with a patent surgical bypass of the obstruction of the left anterior descending artery Hence the reversal of the exercise ECG changes in this patient after successful coronary artery surgery tends to support the conclusion that there is a strong association between exercise induced S-T- egment elevations and severe obstruction of the major compatible coronary artery Also it tends to support the suggestion that exercise induced left axis shifts may be associated with severe obstruction of the left anterior descending artery

Summary

The exercise ECG s and coronary arteriograms of 158 patients were examined to evaluate the relationship of exercise induced axis shifts and S T-segment elevations to coronary artery disease Eighteen of the 158 patients had exercise induced S T-segment elevations Seventeen of these 18 patients had severe obstruction of the major coronary artery most compatible with the zone of ischemic localization This

obstruction was greater than 85 per cent in 16 patients and greater than 50 per cent in a seventeenth patient The remaining patient had a normal coronary arteriogram and the most minimal exercise induced S T-segment elevations *Nine of* the 158 patients had exercise induced right axis shifts. *Only 4 of these 9 patients had* greater than 50 per cent obstruction of a major coronary *artery* as compared to 103 of 154 patients in the total group studied *Also there was no trend toward predominant* involvement of any particular *coronary artery in these 4 patients* Hence it appears that this finding is not predictably associated with severe localized coronary artery disease Only 4 of the 158 patients had exercise induced left axis shifts Three of these four patients had complete obstruction of the left anterior descending artery But the group size was small and the fourth patient had a normal coronary arteriogram Hence it is only possible to suggest that this finding may be associated with severe disease of the left anterior descending artery The results of coronary artery surgery are discussed in a patient who had both a left axis shift and precordial S T-segment elevations on his preoperative exercise ECG

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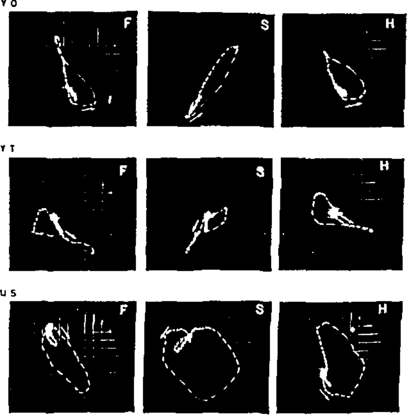


Fig 2 Vectorcardiograms of three patients demonstrating intraventricular conduction defects of varying degrees F = frontal plane S = sagittal plane H = horizontal plane

Table I Electrophysiological findings

Patient	Age yr	Sex	ECG					HBE		VCG
			PR interval (sec)	QRS duration (sec)	Electrical axis	Low P	Others	A H interval (msec)	H V interval (msec)	Frontal QRS loop
Y O	37	M	0 32	0 14	−50°	+	Bradyarrhythmia	128	88	Early forces directed left inferiorly with main forces superiorly terminal delay
Y T	34	M	0 24	0 09	+80	+	Incomplete R B B B	160	44	Terminal delay
U S	45	M	0 20	0 08	+75	−		100	56	Slight terminal delay

the same right femoral vein where a Damato hexapolar probe had been previously introduced The cutting claw was advanced to the apex of the right ventricle under fluoroscopic observation One of the biopsy specimens was fixed in ten per cent formaldehyde solution and stained with the hematoxylin and eosin For electron microscopic examinations an additional specimen was immediately fixed with two per cent phosphate buffered osmium tetroxide for two hours After dehydration with increasing concentrations of alcohol the tissue was embedded in araldite M and sectioned with a microtome Thin sections were stained with uranylacetate alone and

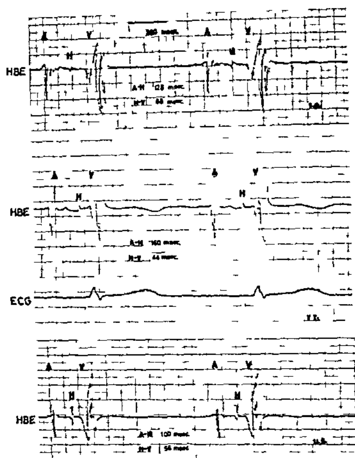


Fig 3 His bundle electrograms from three patients showing atrial (*A*) His bundle (*H*) and ventricular (*V*) potentials and A H and H V intervals Simultaneous recording of HBE and ECG is shown in the middle (patient Y T)

in combination with lead citrate Micro graphs were taken with a JEM 7 electron microscope

Results

Physical examination of the heart re vealed no change among the three patients None of the three claimed to have experi enced symptoms of angina pectoris X ray examination of the chest revealed minimum cardiomegaly in patient Y O Moderate hypotension was present in all three cases Two cases (patient Y O and patient Y T) were found to have electrocardiographic abnormalities as shown in Fig 1 and as listed in Table I

Vectorcardiographic abnormalities were found definitely in two cases (Fig 2) In patient Y O the frontal QRS loop presented initial forces directed left infer iorly with main forces directed superiorly and the delay of the terminal portion The patient s ECG showed left axis deviation (−50 degrees) the prolonged PQ interval (0 32 sec) the prolonged QRS complex (0 14 sec) and the deep S in V_5 and V_6 Conduction delay of the terminal portion of the loop was also found right posteriorly in patient Y T whose standard ECG showed rSR in V_1 and a slightly prolonged QRS complex In patient U S the vector cardiographic tracings revealed slight con duction delay of the terminal portion

Tracing of the HBE was made at one s own sinus rate Electrical activity of the His bundle appeared as a diphasic or triphasic wave occurring between the atrial and ventricular electrograms Fig 3 illus

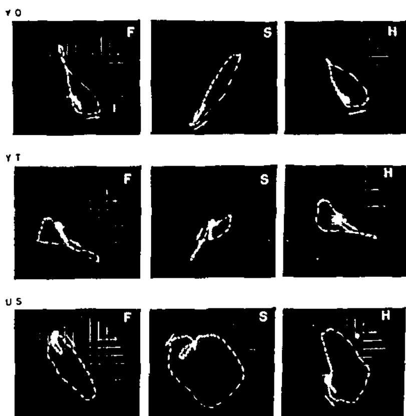


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Table I. *Electrophysiological findings*

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			PR interval (sec.)	QRS duration (sec.)	Electrical axis	Low P	Others	A-H interval (msec.)	H-V interval (msec.)	Frontal QRS loop
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U. S.	45	M	0.20	0.08	+75	−		100	56	Slight terminal delay

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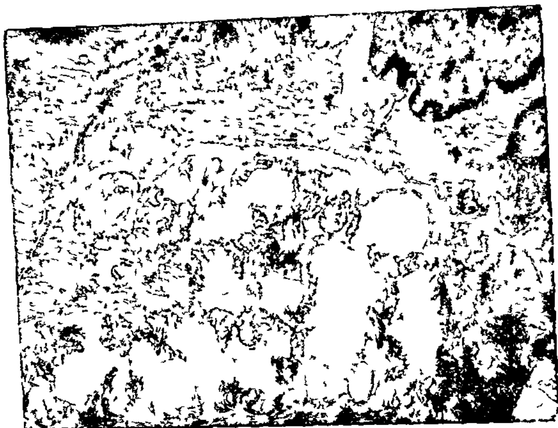


Fig 5 Electron micrograph (patient Y O) Numerous degenerated mitochondria of which membrane is double on one side but single on the opposite side Granular substance appears to have bulged out into the outer space and to be surrounded by the inner and outer membrane (Original magnification ×10 000)

trates the HBE obtained from the three patients Simultaneous recordings of the HBE and Lead II ECG are shown in the middle (patient Y T) The A H interval of the three patients were 128 160 and 100 msec and the H V interval 88 44 and 56 msec respectively

The light microscopic photographs of biopsied myocardium (Fig 4) showed wide variations of heart muscle cells in size and massive infiltration of fatty tissue The nuclei were uneven and some of them were rectangular Alterations in the arrangement of muscle fibers were evident on the longitudinal sections Focal vacuolar degeneration of myocardial cells was seen in transverse sections There was neither fibrosis nor increase in cellularity apart from scattered focal hemorrhages Endomyocardial fibrosis and fibroelastosis were not found

The prominent myocardial changes revealed by electron microscopy in patient Y O were the degeneration of the mitochondria with disorganization of internal structure Degenerated mitochondria were bounded by double limiting membrane on one side but by single membrane on the opposite side Granular substance which was less electron dense was found scattered in the outer space (Fig 5) The majority of mitochondria, however appeared to be essentially normal in patient U S Myofibrillar alterations characterized by disarray and dissolution of the Z line and I band were often found There was also focal contractile element damage with disorganization and loss of myofilaments The external lamina generally appeared to be intact

Patient Y O who had been treated for neurological rehabilitation in Kagoshima University Kirishima Branch Hospital was taken to our department because of syncopal episodes with bradyarrhythmia



Fig 4 A and B A Light micrograph of myocardium of right ventricle of patient Y O B Micrograph of patient U S Note wide variation of muscle fibers in size and massive involvement of fatty tissue The nuclei are uneven and some of them are rectangular (Hematoxylin and eosin Original magnification A ×160 B ×400)

conduction system in a case showing atrial flutter with varying degrees of A V block but found no anatomic basis for the electro cardiographic abnormalities In Thomson s study[18] the S A node was involved by virtue of the site of the atria and the A V node was also affected though to a lesser extent than the S A node Furthermore it is worthy to mention that the bundle branch was involved in an extensive area of myocardial change This denotes the prolongation of H V interval which means the conduction disturbances distal to the His bundle Intraventricular conduction defects of varying degrees were also shown by vectorcardiographic tracings Conduction delay of the terminal portions was oriented superiorly from the point of origin

In 1964 Petkovich and colleagues[19] reported a case of myotonic dystrophy that developed Stokes Adams syndrome due to A V dissociation. An implantation of a pacemaker allowed them to carry out myocardial biopsy taken from the pericardium and they found rather indistinctly bordered myocardial muscle fibers feathery cytoplasm and longitudinal separation of myofibrils In postmortem cases microscopic changes of the heart were fatty infiltration of the myocardium interstitial fibrosis of varying cellularity and sometimes with lymphocytic infiltration[11,17,18,21] The myocardial findings of our cases were almost similar to theirs except for cellular involvement It has been accepted that the classical histological finding of the hearts in myotonic dystrophy was non specific[17,18]

Recently Bulloch and co workers[22] reported electron microscopic changes of the left ventricular muscles of a patient with marked cardiomegaly The most frequent myocardial abnormalities were found in the sarcoplasmic reticulum and mitochondria in cells that otherwise appeared intact In our cases the most striking abnormalities were found in the mitochondria The internal structure was lost and a peculiar substance which was granular appeared to have bulged into the outer space It was not always possible to be sure whether this finding might be a primary site of pathologic change Serial biopsy studies in various stages of the disease are necessary for the detection of early abnormality

Örndahl and colleagues[4] found out by vector and scalar-cardiographic studies that the diffuse change of the specialized conduction system was more dominant than the disorganization of the contractile elements of the myocardium Our results of examination using light and electron microscopy of the biopsied myocardium showed the presence of distinctive involvement of the myocardium It seems therefore likely that both the conduction system and the myocardium are extensively involved in an advanced stages of myotonic dystrophy

The pacemaker implanted in patient Y O has been working well for more than twelve months, but we are pessimistic about this patient s future because of the involved serious cardiomyopathy as revealed by biopsy His younger sister who was suspected to have myotonic dystrophy died accidentally when she was asleep five days after an operation for cataract We had still another patient who died suddenly while waiting for hospitalization Other cases of an unexpected death[3,11,21] were also reported Careful attention should be paid not only to neuromuscular defects and infections but also to cardiac lesions in myotonic dystrophy

Summary

For frequent complications of cardiac involvement it is important to recognize exactly myotonic dystrophy from a cardiovascular standpoint Electrophysiological and histological studies were performed in three patients Analysis of the site of the conduction disturbances was revealed by His bundle electrography proximal to the His bundle in one patient and distal in two other patients The histological examination for biopsied myocardium by light and electron microscopy disclosed replacement of large areas by fat and also showed varying degrees of cellular damage The most striking abnormality of the heart muscles was found in the mitochondria in which a peculiar and granular substance bulged into the outer space Both the conduction system and the myocardium were involved in our cases The value of His bundle recordings and endomyocardial biopsy in evaluating cardiac abnormality in the disease were discussed

Eight days later he developed Stokes Adams syndrome due to cardiac arrest for more than three minutes, from which he recovered with the administration of intra venous isoproterenol On his twenty third hospital day, the electrode of a permanent cardiac pacemaker (ventricular inhibited type) was anchored to the epicardium over the outflow tract of the right ventricle Seven days postoperatively, it was found that a segment of the skin overlying the pace generator was necrotic An ECG made after the implantation of the pacemaker showed natural, fusion, and pacemaker induced beats The induced QRS complexes had the appearance of those of left bundle branch block

Discussion

Myotonic dystrophy, originally described by Steinert,[10] is a heredo familial neuro muscular disease in which cardiac involve ment is common and serious In most cases, neuromuscular defects are apparent long before any evidence of the heart disease but in a few cases the latter may be the predominant feature and an important aid to the early diagnosis [2 11 12] Griffith[1] pro vided a clinical description of a patient with a heart rate of 46 to 30 per minute and was the first to call attention to the disturbances of cardiac rhythm in associa tion with this disease Since then some in vestigators have described cardiac mani festations in myotonic dystrophy There were few clinical signs of the heart disease the most prominent findings being electro cardiographic abnormalities such as vari ous kinds of arrhythmias and conduction defects [3 4 13] The incidence of electrocar diographic abnormalities was reportedly found in 40 to 85 per cent, but cases of complete atrioventricular dissociation with Stokes Adams attacks were rarely docu mented [19 20] The pathogenesis of cardiac alterations, however, remains obscure To our knowledge the present communication is the first in reporting the use of the His bundle electrogram for the determination of the site of conduction disturbances and endomyocardial biopsy for the histological investigations of the abnormalities of con tractile elements

The PR interval was found prolonged for more than 0 2 sec in two cases Payne and Greenfield[13] reported prolongation of the PR interval in five of 21 cases and Örndahl and associates[4] in 11 of 29 patients The standard electrocardiogram however, fails to localize the site of delay or block precisely because the PR interval merely represents the sum of intra atrial conduc tion time through the A V node the His bundle, the bundle branches and a part of the Purkinje fibers The technique of HBE recently developed by Damato and col leagues[14] have contributed to our under standing of the modes of transmission of the impulses from the atrium to the ven tricle Based upon the normal range re ported by Narula and associates [15] pro longation of the A H interval was found in patients Y T and Y O, and that of the H V interval in patients Y O and U S According to Rosen and co workers,[16] most patients with the prolongation of the PR interval and the intraventricular conduc tion defects had the prolongation of P H (the interval from the P wave to the first high frequency component of the H wave) suggesting the lesion proximal to the His bundle In patient Y O whose QRS dura tion was also prolonged both A H and H V intervals were prolonged The latter was more prolonged and the major site of delay was suspected to be distal to the His bundle In fact he soon developed Stokes Adams attacks due to simultaneous atrial and ventricular standstill The lesion was suspected to be proximal to the His bundle in patient Y T In patient U S, the H V interval was found prolonged although his PR interval and QRS complex were normal This finding suggests that there was a first degree block in the distal portion of the main stem of the His bundle below the site of His bundle recording It seems likely that not only the proximal but also the distal region to the His bundle was involved in myotonic dystrophy When first seen, all cases were found progressed showing typical features of the disease so the early cases may allow us to determine whether progression of conduction disturbances occurs either proximally or distally to the His bundle

Histological changes in the specialized conduction system in myotonic dystrophy were reported by a few investigators Can non[17] attempted to study the lesion of the

Immunologic findings in idiopathic cardiomyopathy
A prospective serial study

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Idiopathic cardiomyopathy (I C) is a disease of unknown etiology with suspected immunologic mechanisms[1,3] Serum factors reactive to heart muscle constituents have been reported in between 11 and 30 per cent of sera from patients with I C[1,4,6] Bound gamma globulin[7,8] and complement (C3)[8] have been found in the ventricular muscle of patients who died with this disease the hearts of control subjects being free of such deposits Previous studies have not clarified whether these findings were primary and related to etiology and/or pathogenesis or secondary and represented a nonspecific immunologic response to heart muscle damage

In many diseases with immunologic mechanisms serologic factor titers vary and are often correlated with disease activity In systemic lupus erythematosus where renal and skin manifestations are related to the deposition of antibody antigen complexes the titer of anti D N A antibody parallels disease activity and during a remission the antibody response may be absent or in a low titer[9] Serum complement levels fall just prior to and in relation to an exacerbation of renal disease in systemic lupus erythematosus[9]

Serial studies of sera in acute rheumatic fever have shown heart reactive factors (H R F) in 25 to 63 4 per cent of patients and their presence has been correlated with the development and recurrence of clinical symptoms[10,11] Bound gamma globulin has been found in 18 per cent of auricular biopsy specimens from patients with clinically inactive rheumatic heart disease[12] Sixteen per cent of patients with chronic rheumatic heart disease were found to have H R F[10]

We have previously reported the results of an immunologic study of patients with I C[1] Thirty three patients were subjected to a single study but the data did not show a high incidence of serologic immune factors The present study was undertaken to evaluate serially the presence of humoral immune factors in a group of patients with idiopathic cardiomyopathy and to attempt

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Table I Immunologic data and temporal correlation of positive tests to congestive heart failure in 32 patients with idiopathic cardiomyopathy

Test	Positive	Negative	Temporal correlation of positive tests to cardiac decompensation
H R F	9	23	2
A N A	0	32	0
Latex test for R F	9	23	2
S S C A T	0	32	0
Depression of complement (C3)	1	31	1
Elevation of A S O titer	3	29	0
A T A	6	26	2

Abbreviations H R F = heart reactive factor A N A = antinuclear factor R F = rheumatoid factor S S C A T = sensitized sheep cell agglutination test A S O = antistreptolysin O A T A = thyroid antibody

Other serologic tests The following procedures were performed on all sera (1) rheumatoid factor (anti gammaglobulins) by the Latex Fixation Test (Hyland Slide Test) and Sensitized Sheep Cell Agglutination Test (S S C A T)[14] (2) standard tests for syphilis (3) total serum proteins with albumin globulin ratio (4) serum immunoelectrophoresis (I E P A) (5) thyroid antibodies by the thyroglobulin agglutination test (Hyland Slide Test) and indirect immunofluorescent test for microsomal antibodies[15] (6) anti nuclear factor by an indirect immunofluorescent test on infant thyroid (7) Antistreptolysin O (A S O) titer and (8) serum enzyme battery including lactic dehydrogenase creatinine phosphokinase and glutamic transaminase

The Latex Slide Test was read on a scale of 1+ to 4+ and only tests that are 2+ or greater are reported as positive The I E P A was read on a scale of 1+ to 4+ by a single individual Only elevations or depressions of 2+ or greater are reported as positive

All serologic tests were performed 3 to 4 times a year during periods of stable heart disease at the onset of exacerbation of congestive heart failure and at more frequent interval during severe congestive heart failure

Results

Nine of the 32 patients had positive H R F tests and in eight of the nine it was present on more than one occasion Two patients demonstrated sarcolemmal subsarcolemmal (SS) staining one patient showed only intermyofibrillar staining (IMF) and six patients showed both SS and IMF staining In two of the nine patients there was a correlation between the appearance of H R F and exacerbation of the patient s congestive heart failure In the other seven patients there was no correlation Three patients demonstrated elevated A S O titers but in none of these was H R F present Hyperglobulinemia was noted in eight of the 32 patients but in only one patient did the appearance of hyperglobulinemia correlate with an exacerbation of the patient s congestive heart failure Antinuclear antibodies were not detected Nine of the 32 patients had positive latex slide tests during the course of the disease and in two of these the appearance of the positive latex test correlated with an exacerbation of the patient s congestive heart failure No patient with a positive latex test had a positive S S C A T Six of the 32 patients had positive antithyroid antibody tests and in two of these there was correlation with the onset of congestive heart failure Two had a positive standard test for syphilis (V D R L) one being a biologic false positive Elevated serum enzymes were noted in nine of 32 patients and in two of these there was correlation with increasing congestive heart failure One patient had a preterminal depression of C3 These results are summarized in Table I

Table II correlates the positive serologic findings with changes in the patient s clinical status Five of the 18 patients with stable heart disease had positive H R F

to correlate changes in immunologic variables with exacerbations and remissions of disease The serologic factors studied included anti gammaglobulin and anti nuclear factors (A N A) thyroid antibody (A T A) immunoglobulin and complement levels, and serum H R F

Materials and methods

Patient selection The diagnosis of idio pathic cardiomyopathy is in many respects a diagnosis of exclusion Patients entered into this study were evaluated 3 to 4 times a year with a physical examination chest x ray, and electrocardiogram Peri odic phonocardiograms, vectorcardiograms and cardiac fluoroscopies were performed and several of the patients had cardiac catheterization studies All patients demon strated cardiac enlargement at some time during their clinical course Each patient had either a ventricular or atrial gallop or a summation gallop during periods of con gestive heart failure All patients had abnormal electrocardiograms No patient was included who had a history of angina pectoris myocardial infarction or electro cardiographic evidence of previous myo cardial infarction Patients with a sustained blood pressure of 150/100 mm Hg or more were considered to have hypertensive cardiovascular disease and were not in cluded in this study A diastolic cardiac murmur, valvular calcification diabetes mellitus hypercholesterolemia or hyper thyroidism excluded patients from this study No patient had evidence of idio pathic hypertrophic subaortic stenosis A total of 38 patients satisfied these criteria and were placed in the prospective study Three patients were lost to follow up and three subsequently showed evidence of another etiology for their heart disease

Thirty two patients were followed for a period of 51 6 patient years Twenty two of these were observed for over 1 year and 11 were observed for over 2 years Of the 32 patients four died and the three who were autopsied had findings consistent with idiopathic cardiomyopathy Ten had an exacerbation of disease with new or more severe congestive heart failure on physical examination and cardiac enlargement on chest x ray Eighteen had stable heart dis ease There were 20 men and ten women Twenty four patients were black and eight were white The mean age at onset was 36 5 years All patients were questioned as to possible triggering mechanism of the first bout of congestive heart failure Seven had a daily alcohol intake that exceeded two ounces of hard liquor per day Six had a flu like syndrome prior to the onset of congestive heart failure Five developed congestive heart failure during the first three months postpartum One developed congestive heart failure following a flu like syndrome and also had a history of alco holic intake No triggering mechanism was elicited from the remaining 12 patients

Heart tissue Samples of right ventricular muscle were obtained during cardiac sur gery from a patient with tetralogy of Fallot These were quick frozen in liquid nitrogen and stored at −40° C The tissue was tested for antigenicity with known positive and negative sera before being used in this study

Antisera Goat antisera to human im munoglobulins was prepared and conju gated with fluorescein isothiocynate by the methods previously described[10]

Staining procedure Tissue sections were cut at 5 micra fixed in acetone for 10 minutes at room temperature air dried and rinsed in buffered saline and incubated with test serum for 1 hour The slides were then washed in buffered saline incubated with conjugated goat anti human gamma globulin for 1 hour again washed in buf fered saline and mounted in buffered glycerol Each run contained positive and negative control sera Less than 5 per cent of normal sera give positive reactions The sections were examined with an American Optical Fluorostar Microscope equipped with an Osram HBO 200 Mercury Lamp 2 mm Corning 5840 filter and a red ex cluding BG 14 filter The slides were read independently by two observers without knowledge of the source of the serum being tested The degree of fluorescence was graded on a 0 to 4+ scale 2+ fluorescence being required for a positive reading All positive sera were rerun in dilution Three patterns of immunofluorescent staining of cardiac myofibers were seen sarcolem mal subsarcolemmal (SS) intermyofibrillar (IMF) and diffuse (D)

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Table II Correlation of positive serologic tests with changes in the patient's clinical status in 32 patients with idiopathic cardiomyopathy

Test	18 patients with stable heart disease	10 patients who developed C H F*	4 patients who died
H R F	5	3	1
A N A	0	0	0
Latex test for R F	4	3	2
S S C A T	0	0	0
Depression of complement (C3)	0	0	1
A T A	2	3	1

*C H F = congestive heart failure Other abbreviations same as in Table I

Table III Heart reactive factor titers in 9 patients with idiopathic cardiomyopathy

Patient No	Cardiac status	Titer of heart reactive factor			
		1 1	1 5	1 10	1 20
1	Borderline C H F *	1+	1+	0	0
	Severe C H F	2+	1+	±	0
2	Borderline C H F	2+	1+	±	0
	Mild C H F	2+	1+	0	0
3	Compensated	2+	1+	±	0
	Moderate C H F	2+	±	0	0
4	Compensated	±	0	0	0
	Mild C H F	3+	1+	0	0
5	Borderline C H F	2+	0	0	0
	Borderline C H F	2+	0	0	0
6	Compensated	2+	1+	0	0
	Compensated	2+	0	0	0
7	Acute onset C H F	0	0	0	0
	Compensated	2+	0	0	0
8	Compensated	1+	0	0	0
	Compensated	2+	0	0	0
9	Compensated	2+	0	0	0
	Compensated	2+	0	0	0

*C H F = congestive heart failure

four had positive latex tests and two had positive thyroid antibody tests Three of ten patients with increasing congestive heart failure had positive H R F, and in two there was correlation between the appearance of H R F and an exacerbation of heart failure Three had positive latex tests and three had thyroid antibodies, the appearance of these positive tests usually did not correlate with a change in the patient's clinical condition One of the four patients who died had a positive H R F but there was no correlation between its appearance and exacerbation of the patient s disease

Table III demonstrates the H R F titers on the nine positive patients and correlates these with the patient s clinical condition H R F is present in low titer in patients with I C and a meaningful correlation does not appear to exist between titer of H R F and severity of the disease

There was no correlation between positive *latex tests* and positive tests for H R F or between positive thyroid antibody and H R F tests

Of the nine patients with H R F four had a daily alcohol intake that exceeded two ounces of hard liquor per day two had a flu like syndrome preceding the onset of congestive heart failure one had drug toxicity preceding the onset of congestive heart failure and no triggering mechanism could be elicited in the remaining two patients

Discussion

Twenty eight per cent of patients with idiopathic cardiomyopathy were found to have serum factors reactive to cardiac myofibers at some time during their disease The appearance or disappearance of these factors did not correlate in this study with exacerbation or remission of disease If H R F were to be important in the pathogenesis of idiopathic cardiomyopathy we might expect a positive correlation analogous to anti D N A antibody and renal disease in systemic lupus erythematosus but this was not found Patients with H R F did not have an elevated A S O titer thus making it unlikely that the H R F is a cross reacting antibody to the streptococcus When present H R F was in low titer in patients with and without exacerbation of disease and did not correlate with severity of disease The observations are best explained by considering the H R F to be a secondary phenomena produced in response to breakdown of cardiac myofibers after injury to heart muscle

Twenty eight per cent had a positive latex test but none had a positive S S C A T test Nineteen per cent had positive thyroid antibody tests These percentages are significantly higher than controls none of the patients had evidence of thyroid disease or collagen diseases None of the patients were over the age of sixty The results did not correlate with exacerbation and remission of the cardiac disease and are likely a non specific response to the basic disease process

Twenty five per cent *of the patients* with idiopathic cardiomyopathy had non specific immunoglobulin elevations These were generally found in those patients with more severe disease and increasing congestive heart failure Several of these patients had congestive hepatomegaly and this might account for some of these elevations Serum complement as estimated by C3 on immunoelectrophoretic analysis was normal in all sera except one

There was no correlation between H R F and positive latex tests or positive anti thyroid antibodies Antinuclear factor was not detected at any time during the course of the disease This is worth noting because of the high incidence of antinuclear factors in a large number of autoimmune diseases

Several groups have searched for heart reactive antibody *Robinson* and co workers[4] noted an 11 per cent incidence of heart reactive antibody and Fletcher and Wenger[5] found that the frequency was not significantly different from that of a mixed control group Das and co workers[6] using an indirect immunofluorescent method found heart reactive antibody in 6 of 35 patients (17 per cent) with idiopathic cardiomegaly 7 of 8 patients (88 per cent) with idiopathic hypertrophic subaortic stenosis and in 1 of 43 control subjects

In a previous study from this center[1] H R F was found in only twelve per cent (12 per cent) of patients studied Only 12 5 per cent had positive latex tests and one patient had anti thyroid antibody The higher percentages of positive findings in the present study point out the importance of serial studies as opposed to the single sample study One of the patients who lacked H R F in the previous study has subsequently developed H R F

This prospective serial study of the humoral immunologic findings in 32 patients with idiopathic cardiomyopathy like the previous study does not support the concept that immunologic mechanisms are of pathogenetic significance in this disease Secondary immunologic phenomena are present in I C and are likely to be non specific

Summary

Thirty two patients with idiopathic cardiomyopathy were followed for 51 6 patient years and evaluated for evidence of immunologic disease Serologic and immunologic variables were correlated with exacer

bation and remission of the underlying disease Twenty eight per cent of patients had H R F and 28 per cent had positive latex tests Nineteen per cent had positive thyroid antibody tests There was no correlation between positive tests and the clinical course or between positive tests and the severity of the disease The results suggest that idiopathic cardiomyopathy is a disease in which secondary immunologic mechanisms are present but that they do not play a role in etiology or pathogenesis

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The use of radio-iodinated toluidine blue for myocardial scintigrams*

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Although heart disease is the principal cause of death in many countries and its diagnosis is of major importance methods for direct visualization of the myocardium in intact subjects are few The roentgenogram of the heart shows the *myocardium plus other tissues* especially the blood contained in the cardiac cavities as a single shadow Various techniques show cavities and vessels rather than the myocardium itself On the basis of the important earlier studies which had demonstrated myocardial uptake of potassium and its analogues[1] it was possible to develop a method for *myocardial scintigrams*[2] using salts of cesium 131 This method permitted the demonstration of the left ventricular myocardium through the intact chest wall without significant contribution to the image from the cardiac blood pool or adjacent non-cardiac tissues After original development of the technique *in dogs* it was extended to humans and the myocardial scintigram has subsequently been shown capable of demonstrating myocardial infarcts[3,4] aneurysm of the left ventricle[5,6] cardiomyopathies[7,8] neoplasm in the ventricular wall[10] and rejection of the transplanted heart[11]

However the long biologic half life of cesium creates difficulties not only from the standpoint of radiation dose but also through interference with performance of serial scintigram As skeletal muscles retain cesium much longer than cardiac muscle[12,13] the uptake by intercostal muscles interferes with serial myocardial scintigrams during the days that follow injection of a single dose of cesium 131 Moreover its principal emission a 29 4 KEV x ray poses a considerable problem as a result of its low energy and consequent high absorption in tissues Therefore although cesium 131 has proved an important radionuclide by permitting the demonstration of the validity of the myocardial scintigram for diagnosis the general clinical usefulness of the myocardial scintigram would be greatly increased by the availability of a more convenient radioactive compound for this

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purpose Toluidine blue (tolonium chloride) $C_{15}H_{16}N_3SCl$ a phenazathionium dye was found to concentrate selectively in parathyroid glands of dogs and man after intravenous or intra arterial injection[14] Toluidine blue has subsequently been found to concentrate heavily in myocardium of dogs after intravenous injection[15] Iodotoluidine blue, labeled with iodine 131 or iodine 125 was suggested as a potential radioactive imaging agent for parathyroid scintigrams on the basis of such distribution studies[16] Moreover a preliminary study[17] showed that unlabeled toluidine blue (hereafter abbreviated TB) was present in decreased concentration in myocardial infarcts as compared to normal myocardium after intravenous injection in dogs As the possibility of obtaining myocardial scintigrams with a compound of iodine 131 suggested a way of avoiding the problem posed by the weak emission of cesium 131 further investigation of radioactive iodotoluidine blue (hereafter abbreviated as ITB) as a myocardial imaging agent seemed indicated

But initial studies with ITB were reported as discouraging by other authors as they did not confirm a significant selective uptake of ITB by parathyroid glands[18-20] or myocardium[18-20] of rats after intravenous injection of the radioactive compound It is of interest that the use of a preliminary priming or loading dose of the stable compound TB before injection of the radioactive compound ITB was not reported in any of these negative studies

We have now demonstrated in both rats and dogs a significant selective uptake of ITB by myocardium when the administration of this radioactive compound is first preceded by a priming dose of the stable compound TB This uptake by normal myocardium permits demonstration of myocardial infarcts as cold areas of decreased uptake in dogs We have further demonstrated that the major fraction of administered radioactive iodine given as ITB is excreted with sufficient rapidity to give this compound significant advantage over radioactive cesium as a myocardial imaging agent if serial scintigrams are desired

Methods

Toluidine blue (TB) USP was dissolved in isotonic saline solution in appropriate concentrations to provide the required dose when given at a rate of 0 02 ml per minute to rats and 1 ml per minute to dogs Iodinated toluidine blue (ITB) labeled with either iodine 131 or iodine 125 was obtained* in specific activities ranging from 0 3 to 1 2 millicuries per milligram The dose of ITB given as a bolus intravenously, was 60 microcuries per kilogram of body weight and 20 microcuries per kilogram of body weight for rats and dogs respectively Rats used in this study weighed from 153 to 410 grams Dogs weighed from 8 to 17 kilograms

Studies of the effect of priming doses of stable TB on subsequent distribution of radioactive ITB

RATS Forty nine rats were divided into 7 groups of 7 each and were anesthetized with chloral hydrate To establish the effect of TB doses ranging from 0 to 10 mg per kilogram of body weight were administered in isotonic saline through a tail vein at a rate of 0 02 ml per minute over various time periods One group of rats served as controls receiving no TB this control group received isotonic saline alone prior to the administration of ITB Immediately following the completion of the infusion of the priming dose all rats were given ITB The rats were killed 15 minutes after administration of ITB Tissue samples from all major thoracic and abdominal organs including 4 samples of left ventricular myocardium were taken from each rat The samples were weighed and counted in a scintillation detector

DOGS Eight dogs were divided into 4 groups of 2 each Priming doses of TB ranging from 1 mg per kilogram of body weight to 10 mg per kilogram of body weight were given intravenously at an infusion rate of 1 ml per minute over a period of 45 minutes Following completion of the infusion of TB ITB was given intravenously to all dogs The dogs were killed 15 minutes after administration of ITB Tissue samples were taken from all the

*We are grateful to Gerald Bruno of E. R. Squibb and Sons who generously supplied the radioiodinated toluidine blue

major thoracic and abdominal organs including six samples of left ventricular myocardium from each dog The samples were weighed and counted in a scintillation detector

Studies utilizing a fixed priming dose of stable TB Following the experiments described above a standard priming dose of 10 mg per kilogram of body weight given intravenously over a period of 45 minutes was selected Except as otherwise specified all studies described below utilized this priming dose for both rats and dogs The bolus dose of ITB was given immediately after the conclusion of the infusion of TB

Retention of radioactivity by myocardium and whole body of dogs after injection of ITB Eight dogs were divided into four groups of two each Each dog received a priming dose of TB and a subsequent injection of ITB as described above These dogs were killed at periods ranging from 15 to 90 minutes after administration of ITB Tissue samples including six samples from left ventricular myocardium were removed from each dog and were weighed and counted in a scintillation detector

For an estimation of whole body biologic half life of radioactive iodine when given as ITB three additional dogs were given TB and ITB The dogs were housed in metabolic cages excreta were collected and counted daily The dogs were killed from 7 to 11 days later A complete set of over 30 tissues was removed from each dog Appropriate samples were weighed and counted in a scintillation detector Wherever possible whole organs were weighed otherwise the weight of whole organs was estimated from a standard reference table [21]

Two other dogs received TB and ITB They were studied serially by whole body scintigrams using an Ohio Nuclear Scanner with 5 inch crystal 85 hole collimator and scan minification recording attachment permitting automatic reduction of the scintigram to one fifth original size The serial whole body scintigrams were obtained at various times ranging from one half hour to 5 days after injection of ITB

Myocardial scintigrams Eleven normal dogs received TB and ITB Approximately 15 minutes after injection of ITB the dogs were scanned under pentobarbital anesthesia in the supine position with the legs extended In some instances they were subsequently scanned in the left lateral position also For these scintigrams a Baird Atomic Scanner with 3 inch crystal and 19 hole focusing collimator was used The scanning speed ranged from 7 5 to 10 inches per minute with the scanner set for sharp contrast (per cent background setting at 80) Further details of the techniques employed have been previously described [2]

Experimental myocardial infarcts were induced in 11 dogs by ligation of the anterior descending branch of the left coronary artery under sodium thiamylal anesthesia (Except in the two instances noted below none of these dogs had previously been studied among the 11 normals described in the previous paragraph) After ligation of the coronary artery the chest wall incision was closed and each animal was allowed to recover Twenty four hours after coronary artery ligation each dog was again anesthetized using pentobarbital Each dog received 10 mg per kilogram of body weight of TB over a period of 45 minutes followed by 20 microcuries per kilogram of body weight of ITB intravenously as a single bolus dose Fifteen minutes after the administration of the radioactive compound each dog was killed by an excessive intravenous dose of barbiturate Myocardial scintigrams were then performed using the same scanning factors employed for the normal dogs that had been scanned alive After completion of the scintigrams the heart was removed from each killed dog emptied of all blood and scanned again as an isolated organ Samples of auricles right ventricle lung liver rib muscle skin and fat were taken for scintillation counting Three samples of myocardium from areas of anterior left ventricle distal to the site of arterial ligation and three control samples (one from a site proximal to ligation and two from posterior left ventricle areas not dependent upon the ligated artery for their blood supply) were also taken these were each divided to permit histologic examination as well as scintillation counting Further details of the techniques employed have been previously described [2] Three of the 11 normal dogs described above were subjected to coronary artery ligation 4 days

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Studies of the effect of priming doses of stable TB on subsequent distribution of radioactive ITB

RATS Forty nine rats were divided into 7 groups of 7 each and were anesthetized with chloral hydrate To establish the effect of TB doses ranging from 0 to 10 mg per kilogram of body weight were administered in isotonic saline through a tail vein at a rate of 0 02 ml per minute over various time periods One group of rats served as controls receiving no TB this control group received isotonic saline alone prior to the administration of ITB Immediately following the completion of the infusion of the priming dose all rats were given ITB The rats were killed 15 minutes after administration of ITB Tissue samples from all major thoracic and abdominal organs including 4 samples of left ventricular myocardium were taken from each rat The samples were weighed and counted in a scintillation detector

DOGS Eight dogs were divided into 4 groups of 2 each Priming doses of TB ranging from 1 mg per kilogram of body weight to 10 mg per kilogram of body weight were given intravenously at an infusion rate of 1 ml per minute over a period of 45 minutes Following completion of the infusion of TB ITB was given intravenously to all dogs The dogs were killed 15 minutes after administration of ITB Tissue samples were taken from all the

*We are grateful to Gerald Bruno of E. R Squibb and Sons who generously supplied the radioiodinated toluidine blue

*Table II Radioactivity in tissues of dogs given various priming doses of stable toluidine blue before radio iodinated toluidine blue**

Priming dose (mg/kg)	Radioactivity $\left(\frac{\%\ \text{administered dose}}{\text{Gm tissue}}\right)$ in			Ratio of radioactivity	
	Left ventricle (LV)	Blood (B)	Liver (L)	LV/B	LV/L
1	0.78†	0.11	1.28	7.1	0.6
3	1.35	0.10	1.16	13.5	1.2
5	1.61	0.10	1.49	16.1	1.1
10	1.56	0.12	0.98	13.0	1.6

*See text for further details.
†Each value represents the mean of 2 dogs.

cantly ($p < 0.05$) less in rats receiving a priming dose of TB 10 mg per kilogram of body weight over 90 minutes or 10 mg per kilogram of body weight over 180 minutes as compared to controls No other treatment resulted in a significant difference from control values for hepatic uptake The radioactivity of blood followed the pattern seen in liver with significant ($p < 0.05$) decreases in rats receiving priming doses of 10 mg per kilogram of body weight over 90 minutes or 10 mg per kilogram of body weight over 180 minutes as compared to controls

Except for liver uptake by non-cardiac tissues adjacent to the heart was not sufficiently high in rats given priming doses of TB to lead to significant interference with the use of ITB as a myocardial imaging agent (see below)

DOGS As with rats the most important uptake by an organ adjacent to the heart likely to cause interference with the myocardial scintigram was uptake by liver Table II shows the radioactivity in left ventricle liver and blood of dogs receiving various priming doses of stable TB The use of a priming dose increases the ratios radioactivity in left ventricle/radioactivity in blood and radioactivity in left ventricle/radioactivity in liver thus increasing the likelihood of good resolution of the left ventricle by scanning techniques In dogs this effect of a priming dose is chiefly by way of increased uptake by left ventricle

Studies utilizing a fixed priming dose of stable TB

RETENTION OF RADIOACTIVITY BY MYOCARDIUM AND WHOLE BODY OF DOGS AFTER INJECTION OF ITB The concentration of radioactivity in left ventricle of dogs at various times after injection of ITB is shown in Fig 1 The high uptake of radioactivity obtained when a priming dose of TB is followed by ITB does not lead to prolonged retention of radioactivity in the myocardium

From the eight actual measurements obtained during the first 90 minutes after injection the equation shown in Fig 1 was derived * The curve of this equation is also shown in the illustration The uptake at 24 hours after injection calculated from this equation is shown by the dot at the extreme right of Fig 1 A ninth dog was actually studied at 24 hours and the uptake found in this dog is shown by a bar at the extreme right The calculated and determined points agree very well Despite the rapid decay of myocardial radioactivity during the first 90 minutes after injection the ratio of myocardial radioactivity to radioactivity in the blood (not shown in Fig 1) remained >4 at all times during the

*We acknowledge with thanks the assistance of Dr John G Wagner

*Table I Radioactivity in tissues of rats given various priming doses of stable toluidine blue before radio iodinated toluidine blue**

Priming dose (mg./kg.) and duration of infusion	Radioactivity ((% administered dose†)/Gm. tissue) in		
	Left ventricle	Liver	Blood
Saline control	0.34‡	0.81	0.14
5 in 15 minutes	0.49	0.43	0.10
5 in 30 minutes	0.32	0.45	0.09
5 in 90 minutes	0.59	0.44	0.08
10 in 45 minutes	1.20§	0.67	0.10
10 in 90 minutes	0.82§	0.36§	0.06§
10 in 180 minutes	0.78	0.32§	0.07§

*See text for further details
†In this and subsequent tables the administered dose used in the calculation is the number of microcuries given per kilogram of body weight
‡Each value represents the mean of 7 rats
§Differs significantly ($p < 0.05$) from control

after a normal myocardial scintigram had been obtained in the living dogs. Two of these 3 were among the 11 dogs that received a dose of TB and ITB 24 hours after ligation and underwent myocardial scanning after killing. The purpose of sacrificing dogs with myocardial infarcts *before* scanning was to insure that the subsequent scintillation counting of tissue samples would permit comparable data to be obtained among 11 dogs that had all lived 15 minutes after injection of the radionuclide. However, one normal dog that subsequently underwent coronary artery ligation and received TB and ITB 24 hours later was not killed. This permitted a scintigram of the infarct to be obtained *in a* living dog. Although tissue data from this dog could not, therefore, be compared with data obtained from the 11 dogs killed 15 minutes after ITB injection, this additional dog was killed at the conclusion of the myocardial scanning in order to permit histologic confirmation of infarction.

Results

Studies of the effect of priming doses of stable TB on subsequent distribution of radioactive ITB

RATS. Table I compares the distribution of ITB in rats given various priming doses of TB over various periods of time before injection of ITB. Analysis of variance was first performed on all uptakes of ITB by left ventricle to determine whether any significant difference existed among the 7 means—i.e., to determine whether the use of any priming dose significantly increased uptake over control. After this analysis had demonstrated a significant ($p < 0.05$) difference, further analysis was carried out by Duncan's multiple range test to determine which of the means differed significantly from the control. The latter test demonstrated a significantly higher ($p < 0.05$) uptake of radioactive iodine by left ventricle in rats given 10 mg. per kilogram of body weight of TB over a 45 minute period when compared to controls. The respective uptakes were 1.20 ± 0.66 per cent administered dose per gram of tissue and 0.34 ± 0.13 per cent administered dose per gram. Similarly, the uptake by left ventricle in rats receiving 10 mg. per kilogram of body weight TB over 90 minutes (0.82 ± 0.35 per cent administered dose per gram) was significantly ($p < 0.05$) higher than uptake by controls. Uptake by left ventricle of rats receiving 10 mg. per kilogram of body weight over 180 minutes and uptake by left ventricle of rats receiving priming doses of 5 mg. per kilogram of body weight did not differ significantly from controls.

Similar statistical analysis using the multiple range test showed that the uptake of radioactive iodine by liver was signifi-

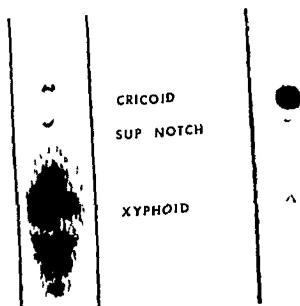


Fig 3 Whole body scintigrams of Dog No 1 given ITB Thirty minute after injection of the radioactive compound scanning started at the head and proceeded caudally The results are shown on the left The scintigram on the right hows the ame do scanned 5 days later

calculation of whole body radiation dose using the formulas of Quimby and colleagues[2] requires an assumption regarding the fate of the 16 per cent which was not found in collected urine stools and residual carcass In the best possible case one assumes that this radioactivity was lost very early after administration of the ITB when small errors in collection of the highly radioactive excreta would result in significant losses In the worst possible case one assumes that the entire 16 per cent was actually in the carcass in addition to the approximately 4 per cent found by analysis Thus in the best possible case a mean of 71 per cent of total radioactivity was excreted as a short half life component with a biologic half life of 0 63 days 25 per cent was excreted with a biologic half life of 28 days and 4 per cent remained to be eliminated by physical decay The respective figures for the worst possible case are 55 per cent 25 per cent and 20 per cent

These data in dogs are useful for estimating expected radiation dose in man following the use of ITB Although species differences obviously may exist and cannot be resolved until studies are conducted in man this preliminary estimation may be of interest The whole body combined beta and gamma radiation dose for a 70 kilogram man receiving 1 microcurie per kilogram of body weight of ITB labeled with iodine 131 after an appropriate priming dose of stable TB is estimated on the basis of the above assumptions as 53 millirads in the best possible case and 73 millirads in the worst possible case

Serial whole body scintigrams of a dog given 10 mg per kilogram of body weight of TB followed by ITB are shown in Fig 3 The scintigrams suggest disappearance of most of the radioactivity from the body within a few days The results obtained in a second dog subjected to serial scintigrams were very similar

Myocardial scintigrams Figs 4 and 5 show anterior views of normal and infarcted myocardium respectively Although our tissue studies have repeatedly shown that uptake by normal right ventricle and atria is comparable to uptake by normal left ventricle the myocardial scintigram results almost exclusively from radiation emanating from the left ventricle as a consequence of the preponderant mass of the latter Figs 6 and 7 show lateral views of normal and infarcted left ventricle respectively These four scintigrams were obtained in 4 different dogs Fig 8 however

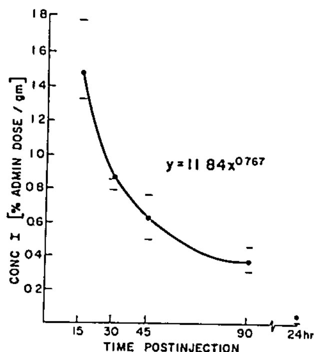


Fig 1 Concentration of radioactive iodine in the left ventricle of dogs at various time after intravenous injection of ITB Horizontal line (—) indicate measured value The dot at 24 hours represents a calculated value See text for details

first 90 minutes The average of this ratio for the eight points during that time was 10 9

The retention of radioactivity in dogs as calculated from daily urine and stool collections is shown in Fig 2 At the time of death the total radioactivity remaining in the carcass of dog A (killed at 7 days) dog B (killed at 10 days) and dog C (killed at 11 days) was 3 28 6 15 and 3 84 per cent of administered dose respectively By the usual curve stripping method the retention curve of radioactivity was separable into two components as shown in Fig 2 The first component had a half life of 0 6 0 6 and 0 7 days respectively in the 3 dogs (mean, 0 63 days) The second component had a half life of 24 32 and 28 days, respectively in the 3 dogs (mean 28 days) Extrapolation of the second component back to the origin indicated that 24 per cent 31 per cent, and 20 per cent of the total dose was retained in the 3 dogs respectively with a mean biologic half life of 28 days In estimating whole body radiation dose we have made the conservative assumption that the residual in the carcass would not have been excreted and would have been lost only through physical decay

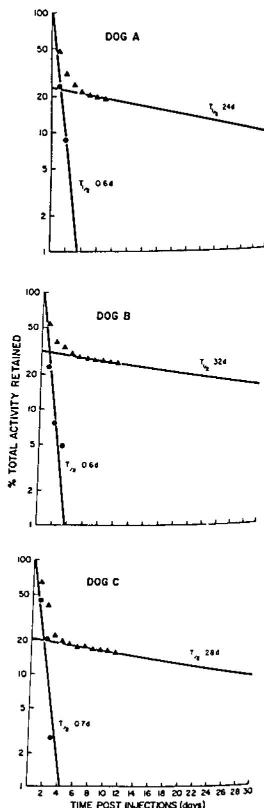


Fig 2 Whole body retention of radioactivity by dogs given ITB

As it was possible to account for a mean of 84 per cent of the administered dose of radioactive iodine through the total collected in urine and stools and the analysis of residual radioactivity in the carcass



Fig 6 Scintigram of a normal dog heart (Dog No 4) Lateral view The priming dose of TB was 5 mg per kilogram of body weight in this dog



Fig 7 Scintigram of Dog No 5 showing a myocardial infarct Lateral view

injection of ITB the mean ratio at time of death *in* these studies was approximately 12 to 1 The scintigram after administration of ITB in these experiments represents primarily radioactivity from the myocardium with little contribution from the low level of activity contained in the blood in the heart cavities This was repeatedly confirmed by scintigrams of the isolated hearts removed from the dog and emptied of all blood The *emptied* hearts gave scintigrams essentially the same as hearts which *contained* blood in their cavities showing normal *left ventricle in* the normal



Fig 4 Myocardial scintigram of a normal dog heart (Dog No 2) Anterior view For this and all subsequent figures a priming dose of stable TB was given intravenously over a 45 minute period followed by a bolus injection of radioactive ITB Scintigram began 15 minutes after the latter injection Except where otherwise specified the dose of TB was always 10 mg per kilogram of body weight and each dog was killed at the beginning of the scintigram



Fig 5 Scintigram of Dog No 3 showing a myocardial infarct Anterior view Infarcts shown in this and all subsequent figures were confirmed by histologic examination

shows anterior scintigrams obtained in the same dog before and one day after experimental myocardial infarction Fig 9 shows lateral scintigrams obtained in still another dog before and one day after experimental infarction Although the ratio concentration of radioactivity in normal left ventricle/concentration of radioactivity in whole blood varies among individual dogs and varies to some degree with time after

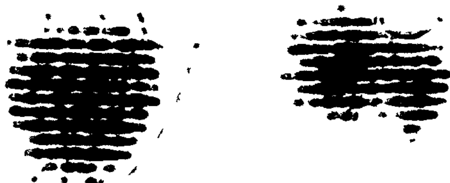


Fig 10 Myocardial scintigrams of isolated hearts *Left* normal heart *Right* heart showing myocardial infarct at the apex A normal dog and a dog with a myocardial infarct respectively each received TB and ITB The respective TB doses were 1 mg per kilogram of body weight and 10 mg per kilogram of body weight Fifteen minutes after injection of ITB the dogs were killed and their hearts were removed After all blood had been emptied from the heart cavities as previously described[22] the hearts were scanned The actual outlines of the heart are projected on the scan The density represents left ventricular muscle

scintigrams may be obtained by repeated doses of ITB even if labeled with iodine 131

Although the rapid disappearance of radioactivity from the myocardium after administration of ITB requires that scintigrams be performed promptly after administration of ITB this has not caused significant problems The radioactivity of the normal left ventricle remains much higher than the radioactivity of infarcted areas or of blood even several hours after administration *of ITB—i e there is a comparable* decline of radioactivity in all three types of tissue Therefore the ratio of radioactivity in target tissue to that in non target tissue the most important factor in permitting a good scintigram remains very favorable for a considerable period of time

Thus the use of ITB offers the possibility of myocardial scintigrams that do not suffer from either of the two disadvantages of cesium 131 weak emission and long biologic half life Cesium 131 has already been shown to be effective in man in demonstrating myocardial infarcts and other myocardial lesions the possibility of obtaining myocardial scintigrams with the more advantageous radioactive compound may significantly improve diagnosis of myocardial infarction in the future and may make it possible to evaluate more precisely therapeutic regimens in myocardial infarction It is of interest that the mean uptake of infarcted myocardium is about 15 per cent the uptake by normal myocardium whether one uses labeled toluidine blue or radioactive cesium

To our knowledge the closest previous approach to demonstration of myocardial infarcts using a compound labeled with radioactive iodine was that reported by *Gunton and associates*[24] *who reported* that oleic acid labeled with iodine 131 could be complexed to human serum albumin and utilized in a technique which according to the authors report just approached the limits of definition of infarction when used for scintigrams in acute cases As noted above iodine 131 is likely to be a very satisfactory label for ITB We have not thus far attempted to use iodine 123 However despite the short physical half life of iodine 123 its emission has a particularly favorable energy (159 KEV) for use with a *radiation camera* Therefore the eventual possibility of using iodine 123 should not be entirely discounted especially if one wishes to use a radiation camera rather than a scanner

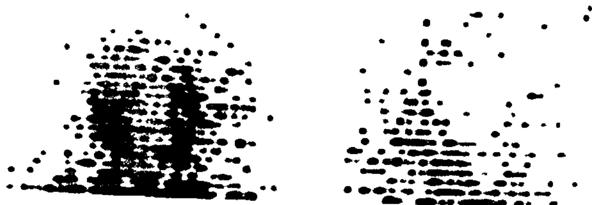


Fig 8 Myocardial scintigrams of Dog No 6 before and after myocardial infarction Anterior view The scan on the left was obtained one day before infarction The scan on the right was obtained 4 days after infarction Both scintigrams were performed in the living dog

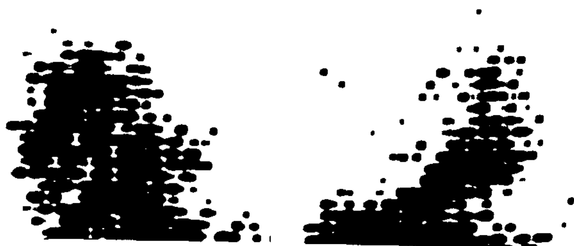


Fig 9 Myocardial scintigrams of Dog No 7 before and after myocardial infarction Lateral view This dog was studied in the same manner as the dog shown in Fig 8 This dog was alive during the performance of the scan on the left and was killed just before performance of the scan on the right

dogs and cold areas of decreased uptake in dogs with myocardial infarcts (Fig 10)

Table III summarizes the data obtained in 11 dogs with myocardial infarctions Actual necrosis of tissue was histologically confirmed in every instance The mean ratio concentration of ITB in infarcts/concentration in normal left ventricle was 0 18 ± 0 31 The difference in uptake by normal and infarced tissue was significant ($p <$ 0 005) by the 't test

Discussion

Both iodine 131 and iodine 125 were used as labels in these experiments in animals The availability of both labels for ITB offers in itself the possibility of serial scintigrams within a short interval of time as one may easily detect iodine 131 while discriminating against iodine 125 The usefulness of both of these isotopes in laboratory animals should not obscure the fact that iodine 131 with its more penetrating emission is likely to be the better isotope in man The emission of iodine 125 would not represent a significant advantage over that of cesium 131, while iodine 131 has a significant advantage in this respect The rapid disappearance of radioactivity through excretion is an additional advantage permitting serial scintigrams without excessive radiation dose The rapid disappearance of radioactivity from the myocardium strongly suggests that serial

Therefore these data are recorded only to suggest that the requirement of a priming dose of stable toluidine blue need not pose an insuperable barrier to the use of ITB as a myocardial scanning agent Although the animal studies reported here are prom ising the authors do not of course advo cate that any initial trial in humans util ze 10 mg per kilogram of body weight as a starting dose regardless of the rate of infusion The same general rules that govern early human trials of therapeutic com pounds must govern trials of diagno tic agents—the initial approach must be cautious utilizing low doses Moreover studies in normal subjects should precede studies in patients

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*Table III Radioactivity in hearts of dogs with myocardial infarcts**

Dog	Uptake† by		Uptake by normal LV / Uptake by infarcted LV	Radioactivity in normal LV / radioactivity in blood
	Normal LV tissue	Infarcted LV tissue		
A§	0 88	0 11	0 13	13 62
B§	0 98	0 10	0 10	13 07
C§	0 30	0 015	0 05	10 24
D	0 28	0 31	1 11	9 83
E	1 48	0 07	0 05	9 16
F	1 22	0 22	0 18	19 67
G	0 87	0 14	0 16	9 34
H	0 93	0 075	0 08	7 15
I	1 36	0 06	0 04	8 80
J	0 51	0 006	0 01	18 92
K	0 29	0 02	0 07	8 29
Mean ± S D	0 83 ± 0 43	0 10 ± 0 09‡	0 18 ± 0 31	11 64 ± 4 23

*Each dog received 10 mg per kilogram of body weight stable toluidine blue over 45 minutes preceding the bolus dose of radio-iodinated toluidine blue Each dog was killed 15 minutes after the latter dose See text for further details.
†Per cent administered dose/Gm
‡Differs significantly ($p < 0\ 005$) from normal left ventricular tissue
§Not the same dogs as dogs A B and C of Fig 2

The mechanism whereby a priming dose of TB first suggested by one of the authors (W DiG) influences the distribution of ITB is at present unknown Both the rate of administration and the total dose of stable TB are significant as suggested by the studies in rats The use of a priming dose of TB does not increase the concentration of radionuclide in important non target tissues (liver and blood) Indeed the data in rats suggest lower radioactivity in these non target tissues as a result of a priming dose of TB It should be noted that the use of a priming dose does not increase the uptake of radionuclide by various other non cardiac tissues after administration of ITB (e g , muscle lung etc) but data on liver and blood have been presented here as they represent particularly important non target tissues in the myocardial scintigram

One may postulate two types of binding site for the phenazathionium nucleus such that one of the sites has a lower capacity but higher affinity than the other Saturation of the first site—e g in liver and blood —by a priming dose of TB might then make more ITB available for the second site in the myocardium Such a mechanism is at present entirely speculative although the reported electrocardiographic changes after an intravenous injection of TB (see below) may be pertinent here

Toluidine blue has been used intravenously in man[14 15 5 6] in the past and has not proved to be a highly toxic compound Kiese and associates gave 4 mg per kilogram of body weight of TB intravenously to humans without ill effect Doses of 6 mg per kilogram of body weight have been given safely to humans intravenously[26] these doses were given over a period of 2 hours Nevertheless rapid infusion of a sufficiently high dose may result in electrocardiographic changes Whereas eight patients studied by DiGiulio and Lindenauer[15] received 5 mg per kilogram of body weight of TB intravenously over periods ranging from 45 to 135 minutes without reported electrocardiographic abnormalities one patient who received 3 5 mg per kilogram of body weight in 30 minutes did show transient depression of the S T segment

The development of cardiac arrhythmias after diagnostic procedures is by no means unknown and even the barium enema is not innocuous in this regard[27] but particular caution is clearly needed to avoid precipitating cardiac arrhythmias in patients already suffering from myocardial infarcts

striking that our curiosity was aroused This study has enabled us to define its physiological and clinical significance

Methods

We used a capacitance Brecht and Bouche transducer having a frequency response flat to 200 Hz [8] The transducer was attached to a short rod which projected 1 5 cm beyond a metal circle which surrounded it The tip of this rod placed over a point where maximal pulsation in the carotid had been palpated was pushed down until the circle was in contact with the skin and then it was held firmly in place with a strap around the neck A standard differentiating circuit and two channels of a Sanborn Twin beam recorder were used to record the pulse and its derivative simultaneously The methods of calibrating the pulse derivative (PD) and of measuring the maximum rate of pressure rise (I D max) have been described [4]

Such records were always taken after the supine subjects had rested comfortably for at least 15 minutes Several positions of the transducer were tried in each subject that producing the largest record—i e the record requiring the least amplification being preferred ULF force ballistocardiograms taken simultaneously with the pulse records play a very minor part in this study

When right and left heart catheterizations were performed they were done a day or two before or after the pulse records were taken Pressures obtained at catheterization were inscribed by an Electronics for Medicine DR12 polybeam photographic recorder using a Statham P23 DB transducer The transvalvular aortic gradient was measured during pullback from the left ventricle the systolic mean gradient being recorded We used the conventional 20 mm Hg as the upper limit of normal for the aortic valve gradient

Subjects

The patients studied were adults who had or were suspected of having serious cardiac disease All were inpatients in the University Hospital and all were ambulatory

One hundred-eighty patients were subjected to cardiac catheterization Since the composition of this group was biased by the ordinary criteria for selecting patients for this test a larger and a more representative group of cardiac patients was secured by adding the last 169 cardiac patients studied who had not been catheterized records of their pulse derivatives having been taken in conjunction with ballistocardiographic studies The final hospital diagnosis used to classify each case was made by a doctor without knowledge of our findings in the pulse

Results

What we have called the carotid high frequency abnormality illustrated in Figs 1 and 2 consists of a brief burst of high frequency distortion superimposed on the basic pattern of the pulse derivative for part of the cardiac cycle Usually of 15 Hz or faster the burst starts at or shortly after the main wave s peak and usually lasts from 0 1 to 0 4 second By its regular position at this part of the cardiac cycle the abnormality can be easily distinguished from electrical noise

As shown in Figs 1 and 2 when the abnormality was present and the rhythm regular the general pattern was repeated with every heart beat but there was often some variation in the HF details of the burst Such small differences are probably due to artefacts for slight changes in the exact positioning of the sensor on the artery and in the pressure applied often caused similar changes in the record probably by altering the transmission of the HF vibrations from arterial lumen to sensor No similar bursts of HF distortion have ever been encountered in pulse derivatives secured on healthy persons so the abnormality can be recognized at a glance (Fig 1) Duplicate runs made on the same day or on different days give excellent agreement of the general pattern of the abnormality despite some differences in the HF details

Very conspicuous in the pulse derivative the HF abnormality can sometimes be recognized in the conventional pulse but only if one examines the record very carefully (Fig 1) in the majority of cases it would certainly be overlooked

Table I was compiled from data secured from the 180 patients catheterized There

Disturbed blood flow in the carotid artery: Its physiological and clinical significance

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Elasticity in the rubber membranes, rubber tubing, and air transmission systems used in the early clinical studies of the pulse prevented the proper recording of its high frequency (HF) components, so one cannot expect to find evidence of HF abnormalities in this literature. We know of no mention of such abnormalities *before* 1955, when Smith[1] after improving his apparatus by greatly diminishing the size of his air transmission system described an HF abnormality in the carotid *pulse of a* case of aortic stenosis. Smith also performed a very illuminating experiment on this patient: after he increased the size of his air transmission system until it resembled the apparatus used in early work on the pulse, the HF abnormality disappeared and was replaced by the "bisferiens" type of pulse so often described as characteristic of aortic stenosis in the older literature.[2]

Soon after Smith's study, the use of rigid apparatus in conjunction with electrical methods of transmission and recording provided records in which the HF components of the pulse were much better recorded, and Smith's finding was soon confirmed in several laboratories.[3-7]

In this laboratory increasing interest in the cardiac forces and in incoordination of the cardiac contraction led to continued efforts to improve our knowledge of the HF components of the pulse. Thus since 1959 the pulse derivative has been recorded routinely to bring out HF information and, in 1964, the sensor was shifted from the brachial to the carotid artery to minimize the loss of HF information which occurs as the wave travels down the artery. Since that time, pulse records containing far more HF information than has been recorded in most other clinical studies of the pulse have been secured in over 1,000 subjects, both patients and healthy persons.

Certain of these patients exhibited an HF abnormality of the carotid pulse so

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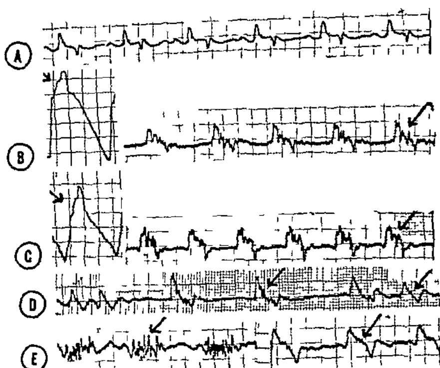


Fig 1 A through E High frequency abnormalities in the carotid pulse Arrows point to features of interest A A normal record for comparison PD max = 680 mm Hg per second B Enlarged carotid pulse (*left*) and pulse derivative (*right*) Patient K V age 18 gradient 32 mm Hg Congenital aortic stenosis aortic insufficiency Grade 2 Note conspicuous HF abnormalities in PD and that they can also be seen in the enlarged conventional pulse PD max = 477 mm Hg per second C Same records of patient F U age 54 gradient 57 mm Hg Aortic stenosis aortic insufficiency Grade 3 Note conspicuous abnormality in PD it is present but almost unrecognizable in the enlarged conventional carotid pulse PD max = 324 mm Hg per second D Carotid PD of patient T R age 73 RHD severe aortic and mitral regurgitation atrial fibrillation gradient variable minimum 10 mm Hg Note HF abnormality in large beat its absence from smaller E Carotid PD (*left*) and brachial PD (*right*) of D C age 33 Aortic stenosis and aortic insufficiency Grade 4 Gradient 80 mm Hg PD max = 248 mm Hg per second Note maximum HF abnormality in carotid PD its almost complete disappearance by the time the brachial was reached

physical facts both a distorted aortic lumen and a flow velocity which exceeds a critical level are needed to produce the bursts of disturbed flow we detect in our patients

Classic physical experiments indicate that similar factors are concerned in the genesis of disturbed flows in tubes [9] Roughness of the wall and irregularities in the shape of the tubes such as narrowing and widening will promote the appearance of turbulence whenever flow velocity exceeds a critical level Nevertheless turbulence as usually defined today is a phenomenon of much higher frequency than our methods of recording the pulse would detect [9] Thus while evidence secured by Doppler techniques[10] indicates that blood turbulence does indeed accompany some cases of aortic stenosis our studies provide no evidence for or against its presence in our cases

So our data suggest that the carotid high frequency abnormality found in our patients is due to a disturbance of flow profile in which normal streamlined flow is interrupted by eddies vortices and jets This abnormality should not be called turbulence but if sufficiently intense it would probably be accompanied by turbulence Such a physiologic abnormality would like turbulence handicap the heart by increasing the impedance to ejection So we have demonstrated that a physiological abnormality of blood flow which handicaps cardiac performance is present in most cases of aortic stenosis

Relation of disturbed aortic flow to ab

Table I. Primary cardiac diagnoses made on 180 patients catheterized and their relation to the carotid high frequency abnormality

Diagnosis	Patients with the HF abnormality (No.)	Patients without the HF abnormality (No.)
Calcific aortic stenosis	5	0
Aortic stenosis (non calcific)	2	2
Subaortic stenosis	1	0
Aortic stenosis and insufficiency	15	1
Aortic insufficiency without stenosis	11	13
Mitral valve disease	7	27
Coronary artery disease	1	57
Congenital septal defect or patent ductus	0	12
Cardiomyopathy	0	6
Hypertensive heart disease	0	5
Congenital pulmonary stenosis	0	3
Other cardiac lesions	0	3
No cardiac diagnosis	0	9

is a highly significant relationship between the presence and absence of the carotid HF abnormality and the normality and abnormality of the gradient, chi square = 63.

The relations between the presence and absence of the HF abnormalities and the final clinical diagnoses in the group catheterized are shown in Table I. In the enlarged group of 349 patients the HF abnormality was present in 89 per cent of 35 cases diagnosed aortic stenosis, in 48 per cent of 29 cases diagnosed aortic regurgitation without stenosis, and in less than 1 per cent of 285 cases diagnosed cardiac disease without aortic valve involvement. It has not been seen in any healthy person.

Obviously there is a highly significant relation between the carotid HF abnormality and aortic valve disease.

Discussion

Relation to the thrill. The genesis of the HF abnormality demonstrated in our patients is surely related to that of the thrill palpable in so many cases of aortic stenosis, but our modern methods detect the abnormality in many cases in which no thrill was discovered at routine examination. Evidently we have a more delicate test than palpation provides.

Genesis of the carotid HF abnormality. An array of clinical evidence indicates that an *anatomical factor* associated with the aortic valve is of prime importance in the genesis of this abnormality. It was very seldom encountered in patients without manifest aortic valve disease. In all four cases in which an aortic valve prosthesis was inserted into a previously stenotic orifice, the HF abnormality disappeared (Fig. 2) or was greatly ameliorated, although lower frequency abnormalities often remained in the pulse record.

But our evidence also points to the importance of a *physiological factor* in its causation. In all cases the HF distortion occurred in only one part of the cardiac cycle, at and after the time of the normal peak of the pulse derivative when ejection velocity would be at its highest (Figs. 1 and 2). In some cases in which the heart beats differed in strength (Fig. 1), the abnormality was present whenever the pulse was large and absent when it was small. In one case (Fig. 3) the HF abnormality disappeared after coronary bypass surgery to reappear after the heart had recovered from the immediate effects of the operation. Such differences are certainly not due to structural changes in an aortic lesion; a physiological factor, such as differences in flow velocity, must be invoked to account for the findings.

One patient later demonstrated at operation to have a tight aortic stenosis never exhibited the carotid HF abnormality. Before operation his PD max was one of the smallest encountered in this study and his cardiac output (dye method) was calculated to be only 1.4 liters/min/M². Apparently his blood velocity was too small to generate the HF abnormality despite the presence of the aortic lesion.

Several cases of wide open aortic regurgitation, whose ejection acceleration must have been very great to account for their large force ballistocardiograms and huge PD max's (Fig. 3), showed no trace of the carotid HF abnormality. Evidently neither a tight stenosis of itself nor a high ejection velocity of itself is sufficient to produce the abnormality. So our evidence leads to a theory which is consistent with well known

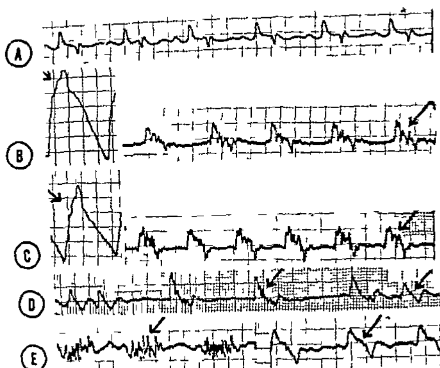


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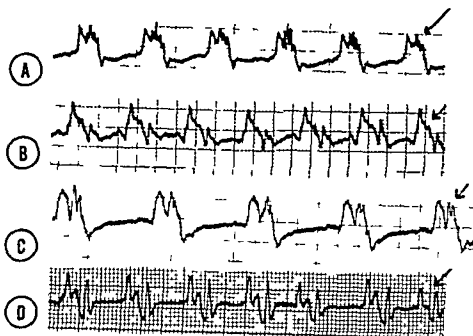


Fig. 2. *A* through *D*. Effect of the insertion of a prosthetic caged ball valve into a stenotic aortic orifice. *A* and *B*. Carotid PD of N. U., age 68. Luetic aortic stenosis and insufficiency. *A*. Before operation, gradient 47 mm Hg, PD max = 421 mm Hg per second. *B*. After operation PD max = 817. Note disappearance of most but not all of the carotid HI abnormality. *C* and *D*. Same records on N. F., age 58. Aortic stenosis, aortic insufficiency, mitral stenosis. *C*. Record taken before operation when gradient = 50 mm Hg and PD max = [illegible]45 mm Hg/sec. *D*. Records taken after operation when PD max was 777 mm Hg/sec. Note that the HI distortion disappears after operation but some low frequency distortion remains.

normal aortic valve gradients. The disturbed flow indicated by the HI abnormality in the pulse is accompanied by an abnormal gradient in almost all our cases. Theoretically the two are related in several ways.

Velocity being constant, abnormal pressure drops across the aortic orifice might conceivably be due to impedance caused by narrowing alone or by disturbed flow alone. In the great majority of our cases the increased gradient was probably due to both factors, how much each contributed being unknown. Impedance due to disturbed flow alone may be larger than most doctors realize. Schultz and colleagues[11] perfused normal and arteriosclerotic abdominal aortas secured at necropsy with a fluid of the same viscosity as blood. In normal vessels the gradient at a velocity of 40 c.c. per second was 2 to 3 mm Hg. But in one sclerotic aorta with a maximum narrowing of only 6 per cent, a gradient of 12 mm Hg was found. Since this amount of narrowing would not cause a detectable gradient increase if produced experimentally in a normal vessel, this fourfold increase of gradient must be attributed to the impedance of a flow disturbed by roughening and distortion of the vessel walls. Obviously the disturbed flow pattern demonstrated in our patients may be an important factor in their disability.

From the physiological viewpoint both gradient and flow disturbance are influenced by blood velocity, but in a different way. Venturi's principle describes the relation of narrowing to the gradient; in this formula velocity appears as a continuous function. In equations describing the relations of turbulence and disturbed flows, velocity is a step function—i.e., the phenomenon appears when velocity exceeds a critical level. So it is easy to see why an abnormal gradient and a disturbed flow are usually associated in our patients and also that they need not always be associated. Our clinical data on the latter situation are of interest.

Discussion of unusual findings. In 17 cases the HF abnormality was present but the pressure gradient across the aortic valve was not abnormally increased. Most of these were cases of aortic valve disease in which regurgitation predominated. Evi

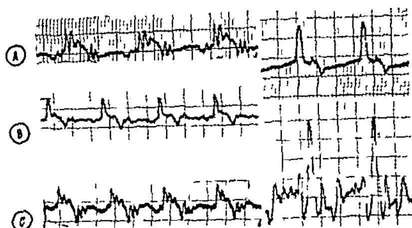


Fig 3 *Left* panel A B and C Factor in the presence or absence of the carotid HF abnormality Carotid pulse derivative of B T age 54 diagnosed coronary heart disease A Before operation note HF abnormalities B Twelve days after coronary bypass operation note disappearance of HF abnormalities C Two month postoperative note return of HF abnormality PD max was 300 276 and 300 mm Hg per second in the three records *Right panel* Carotid pulse derivative over force BCG of N R age 23 wide open aortic regurgitation PD max = 4,500 mm Hg per second which is record breaking Calibration of force BCG 13 small divisions = 275 (10³) dynes So this record is also huge The aortic valve gradient was normal Note that in the presence of what must have been a very great blood velocity HF abnormalities in the carotid PD are absent

dently a roughening without narrowing of the orifice may produce a disturbed flow causing too little impedance to produce gradient abnormality

In five cases the gradient was found to be abnormally increased but no disturbed flow was detected Such findings might have been due to an artefact for which we were on the lookout should any patient be more excited at catheterization than when the pulse derivative was taken such findings might well result However the pulse rates recorded at the two tests were so similar in each of these five patients that it is hard to believe that differences in excitement were the cause of our findings It is easier to believe that the increased impedance in these cases was due to aortic narrowing alone the lesion having so little roughness that a disturbed flow did not accompany it

The possibility that disturbed flow in the carotid might be created without an aortic lesion should also be discussed for we have five cases in which the HF abnormality was present without any clinical evidence of aortic valve disease All these were cases of advanced rheumatic heart disease with several mitral valvulitis To account for murmurs heard in the aortic area when that valve is normal it has been suggested[1] that when blood regurgitates through a deficient mitral valve in sufficient amount the jet strikes the atrial wall adjacent to the aortic arch such a jet might not only produce an audible murmur but might also set up vibrations in the aortic blood which our sensor would detect While one should not forget that an aortic lesion so common in advanced cases of RHD might have been present in these five cases though undiagnosed those doing the catheterization were convinced that this valve was normal

It is also conceivable that small elements of a myocardium which had lost the coordination of its contraction might beat such a rapid tattoo on the ventricular blood that rapid fluctuation of the rate of change of pressure would appear in the carotid High frequency distortions are often superimposed on undamped ventricular pressure records and perhaps too often dismissed as artefacts But we found no evidence of HF distortion in the contour of the ballistocardiograms of any of these cases The common types of cardiac incoordination produce distortions of these records of a lower frequency than those encountered in the carotid HF abnormality

While other possibilities cannot be ruled out at this time the genesis of disturbed

flow in the carotid artery is clearly related to a lesion of the aortic valve in the great majority of our cases

Conclusions

Records of the carotid pulse and its first time derivative have been taken, under standard resting conditions, in 349 cardiac patients, 180 of whom were subjected to cardiac catheterization These results have been analyzed to throw light on an abnormality of pulse contour, conspicuous in the pulse derivative a burst of high frequency distortion occurring at and after the peak of the main wave

The presence of this abnormality is closely related to the presence of aortic valve lesions diagnosed either by the aortic valve gradient or by conventional clinical evidence While such a lesion must be a prime factor in its genesis in most cases the evidence also indicates that a second factor must be present before the abnormality is produced sufficient velocity of the ejected blood This theory is satisfactory in 98 per cent of our cases the few discrepancies are discussed

Such rapid fluctuations in the carotid pulse derivative indicate a disturbance of blood flow in which its normal streamlined character is broken up by vortices jets and eddies Such a disturbance should not be called turbulence because turbulence is defined today as a phenomenon of much higher frequency than our methods would detect The eddies and whorls of such disturbed flows must increase the impedance to cardiac ejection and like turbulence make the heart s task more difficult This handicap is very common in aortic valve disease

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Reciprocal movement of the right and left heart, demonstrated by directional Doppler ultrasound

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Hans R. Muller, M.D.
Philadelphia, Pa., and Basel, Switzerland

The Doppler signals which can be detected over the precordium using an ultrasonic source have previously been described.[1,2] If the difference frequency which lies in the audible range is presented, irrespective of sign, to a zero crossing detector, a characteristic pattern of unidirectional spikes is produced corresponding to wall movement, valve leaflet movement, and blood flow.[3] The advent of directional equipment which has been used by several investigators[4-10] to study peripheral blood flow non-invasively provided us with an opportunity to compare the movements of the right and left sides of the heart.

In the directional instrument,* Doppler shifted frequencies above the 4 MHz center frequency (i.e., movements towards the probe) are fed to one zero crossing detector, while frequencies below 4 MHz (movements away from the probe) are fed to a second detector. The output of the latter is inverted, after which the two are combined to produce a single differential output.

Observations were made on six normal subjects in the supine position. One probe was placed on the precordium just internal to the apex, pointing directly posteriorly, while a second probe was located over the epigastrium, just to the right of the xiphoid process and pointing upwards, backwards, and to the right—i.e., normal to the inferior surface of the right ventricle. Recordings were made simultaneously with the electrocardiogram on a Mingograph electroencephalograph.

During systole, movement towards the probe was detected over the left ventricle. At the same time, over the right ventricle, reciprocal movement away from the probe was recorded. In diastole the direction of the movements was reversed. Fig. 1 shows two representative tracings.

The deflections obtained over the apical area both in systole and diastole correspond in time and direction with the movement of the anterior surface of the heart. On the right side the probe is closer to the base of the heart, which is tethered by its attachments to the great vessels. The inferior surface of the right ventricle would thus be expected to retreat from the anterior chest

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Received for publication J[illegible] 22, 1973.
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The effect of noradrenaline on blood flow and oxygen consumption in normal and ischemic areas of myocardium

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J R Parratt B Pharm M Sc Ph D
Glasgow Scotland

Noradrenaline has been extensively u ed in the management of clinical shock of cardiac origin [1,2] The most likely explanation for any clinical benefit achieved is that by elevating perfusion pressure noradrenaline increases collateral flow through a coronary vascular bed which is often atheromatous [3,5] This would clearly be beneficial to patients whose myocardial performance is limited by a low coronary perfusion pressure Recently Maroko and associates[6] have shown that elevating the systemic arterial pressure (with methoxamine) in dogs subjected to acute coronary artery occlusion markedly reduced ST segment elevation They concluded that elevating arterial pressure decreased the extent of ischemic injury presumably by elevating collateral flow To our knowledge however there have been no studies on the effects of noradrenaline on nutritive blood flow or on oxygen consumption in ischemic areas of the myocardium In the present study a technique has been used which enables simultaneous comparisons to be made of blood flow in ischemic and essentially normal areas of the left ventricular wall Sampling blood from the coronary sinus (draining essentially normal areas of myocardium) and from a coronary vein (draining the ischemic muscle mass) also allowed simultaneous assessments to be made of oxygen consumption by these two areas

Methods

Nine greyhounds of both sexes and weighing between 25 and 34 kilograms were anesthetized with sodium thiopental (20 mg per kilogram of body weight injected intravenously) After endotracheal intubation anesthesia was maintained with 0 5 to 1 0 per cent trichloroethylene (Trilene) vaporized from a Tritec vaporizer (Cyprane Ltd) The dogs were on intermittent positive pressure ventilation with oxygen throughout the experiment the stroke volume of the Palmer ventilation pump was adjusted to give an expired end tidal P_{CO_2} between 26 and 38 mm Hg (arterial P_{CO_2} 30 to 40 mm Hg 1 mm Hg = 1 333 m bar) Reflex movement was prevented by the intermittent administration of succinylcholine (100 mg by intramuscular injection)

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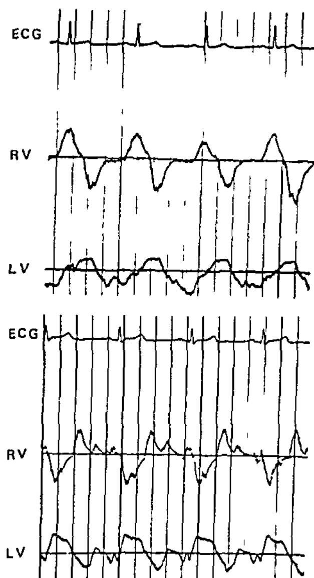


Fig *1 top and bottom* Simultaneous recordings of the electrocardiogram and directional velocity doppler cardiogram recorded over the right ventricle (*RV*) and left ventricle (*LV*) in two normal subjects Movement toward the probe is shown as an upward deflection

wall during systole, and approach it during diastole which is also in accord with the Doppler findings Application of this non invasive directional technique to disorders of cardiac movement is being pursued

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Table I Hemodynamic effects of coronary artery ligation and of noradrenaline infusions (1 0 μg/Kg)/min (mean ± S E n = 12)

	Pre-ligation	*2 to 3 hr post ligation*	*Noradrenaline (2 to 3 hr post ligation)*
Systolic blood pressure (mm Hg)	158 ± 8	151 ± 9	218 ± 9†
Diastolic blood pres ure (mm Hg)	120 ± 5	111 ± 5	157 ± 6†
Mean blood pressure (mm Hg)	135 ± 6	125 ± 7	177 ± 7
Heart rate (beats/min)	166 ± 5	188 ± 10	236 ± 21
Cardiac output (L /min)	3 2 ± 0 4	1 9 ± 0 2	2 4 ± 0 2
Cardiac work (kg M /min)	5 8 ± 0 8	3 4 ± 0 5	6 1 ± 0 7†
Peripheral vascular resistance (arbitrary units)	49 ± 8	71 ± 8	85 ± 11
LVEDP (mm Hg)	10 1 ± 1 6	16 ± 3	20 ± 3
LV dP/dt max (mm Hg ')	1572 ± 154	1591 ± 157	3316 ± 27?†
Left circumflex coronary flow (ml /min)	90 ± 8	79 ± 8	145 ± 13†
Myocardial oxygen consumption (ml /min)	11 7 ± 0 6	11 1 ± 1 3	20 1 ± 1 8†
Myocardial vascular resistance (arbitrary units)	1 4 ± 0 2	1 6 ± 0 1	1 2 ± 0 1
Total body oxygen consumption (ml /min)	—	126 ± 10	112 ± 17

P < 0 05
†P < 0 0005

sentially normal region ml /min) left circumflex flow (ml /min) × arterial – coronary sinus oxygen contents (ml /ml blood)

(2) Myocardial oxygen consumption (ischemic region ml /100 Gm /min) infarct flow ([133]Xenon clearance ml /100 Gm /min) × arterial – coronary vein oxygen content (ml /ml blood)

(3) Myocardial vascular resistance (essentially normal myocardium arbitrary units)

$$\frac{\text{diastolic blood pressure (mm Hg)} - \text{right atrial pressure (mm Hg)}}{\text{mean left circumflex flow (ml /min)}}$$

(4) Myocardial vascular resistance in the ischemic region was separated into two components—collateral (large vessel) network resistance and the resistance of the small vessels in the ischemic region itself (infarct resistance) They were calculated as follows

A collateral resistance (arbitrary units) diastolic blood pressure (mm Hg) – diastolic PCP (mm Hg)/PCF (ml /min)

B infarct resistance (arbitrary units) diastolic PCP (mm Hg) – right atrial pressure (mm Hg)/[133]Xenon clearance (ml /100 Gm /min)

(5) Whole body oxygen consumption (ml /min) cardiac output (ml /min) × arterial – right atrial oxygen content (ml /ml)

External cardiac work peripheral vascular resistance myocardial oxygen availability and oxygen extraction coefficients were calculated as previously described [14] (±) Noradrenaline (1 0 μg per kilogram of body weight per minute as base was infused into a brachial vein using a LKB slow infusion pump (rate 1 0 ml /min) for a period of ten to fifteen minutes two to three hours after acute coronary artery ligation (mean time after ligation 2 hrs 35 min) Twelve experiments were performed in nine dogs All values quoted in the text are mean ± S E Statistical analysis was performed using Student s paired t test

Results

The effects of coronary artery ligation Two to three hours after acute coronary artery ligation the most pronounced hemodynamic changes were decreases in cardiac output and in external cardiac work (Table I) Systemic arterial pressure was maintained despite the reduction in cardiac output by a compensatory increase in peripheral vascular resistance Although left ventricular dP/dt max was unchanged the

Temperature was measured in the mid esophagus using a direct recording thermo couple (Ellab, Copenhagen)

Using a Siemen s image intensifier, cath eters were positioned under fluoroscopic control in the descending aorta, left ven tricle, right atrium and coronary sinus and were used for blood sampling and for pres sure measurements using Elema Schonan der capacitance transducers The rate of change of left ventricular pressure (dP/dt) was measured using an Elema Schonander differentiator circuit and for the measure ment of left ventricular end diastolic pres sure (LVEDP) the left ventricular pres sure pulse was also recorded at high gain and the record cut off above 40 mm Hg Cardiac output was measured by dye dilution Indocyanine green (2 5 mg) was injected into the right atrium and blood was withdrawn from the descending aorta through a densitometer (Waters Co Rochester, Minn)

The heart was exposed through a left thoracotomy the pericardium was incised and the anterior descending branch of the left coronary artery was prepared for liga tion at a position distal to the main septal branch The anterior coronary vein (or one of its major branches) was catheterized using a Longdwel 4 inch Teflon catheter (20G) The catheter was manipulated so that the tip lay well into the potentially ischemic area it was not found necessary to tie this catheter in position After coro nary artery ligation this catheter has been shown to drain blood predominantly from the infarcting area [7,8] Anerobic blood sam ples (2 ml) were simultaneously obtained from this catheter and from the coronary sinus right atrium and descending aorta and were analyzed for Po_2 Pco and pH using appropriately calibrated electrode systems (Radiometer, Copenhagen) as out lined by Ledingham and associates [9] To allow for any difference in the measurement of oxygen tension between gas and blood a blood gas factor was derived for each experiment using blood tonometered with a known tension of oxygen Oxygen and car bon dioxide tensions and pH, were cor rected for any difference in temperature between the electrode and the animals mid esophageal temperature using the Ra diometer blood gas calculator[10] or an ap propriately programmed Hewlett Packard desk computer Hemoglobin was mea sured using a co oximeter (Instrumentation Laboratory Inc , Lexington Mass) and blood oxygen content was calculated using the formula

$$\text{Hb (Gm)} \times 1\ 39 \times \%\ \text{saturation}/100 + Po_2\ (\text{mm Hg}) \times 0\ 0031$$

There is a good correlation between blood oxygen content calculated by this indirect method and by simultaneous Van Slyke determinations [9]

Blood flow in the left circumflex coronary artery was measured using a Nycotron 372 electromagnetic flowmeter and an implant able 2 or 2 5 mm probe The probe was calibrated at the end of the experiment by perfusing the vessel with the animals own blood at known flow rates

After a one to two hour stabilization period during which time several samples were taken for blood gas determinations from each of the four catheter sites (coro nary sinus and vein, right atrium and aorta) an intravenous injection of ligno caine (20 to 40 mg) was given and the left anterior coronary artery was ligated in one stage A Portex nylon catheter (O D 1 34 mm) was inserted distally into the artery and tied in position This catheter was used for the assessment of peripheral coronary pressure (PCP) using a capacitance trans ducer for the measurement of back (retro grade or peripheral) coronary flow (PCF) from the open catheter and for the injec tion of small amounts (about 90 μCi vol ume 1 2 ml) of ^{133}Xenon into the ischemic region The clearance of radioactivity from the ischemic muscle was measured using a collimeter with a narrow angle of accept ance positioned directly over the ischemic region This method of assessing nutritive blood flow in ischemic regions of the myo cardium has been used by a number of workers including Rees and Redding[11] and Gregg[12] and Pasyk and associates [13]

Left circumflex blood flow (phasic and mean) systemic arterial right atrial, left ventricular and peripheral coronary pres sures left ventricular dP/dt and the elec trocardiogram (standard limb Lead II) were recorded on an eight channel Elema Schonander ink jet writing recorder

The following data were derived

(1) Myocardial oxygen consumption (es

Table II Changes in the ischemic myocardium induced by noradrenaline (mean ± S E n = 12)

	Control	*Noradrenaline*
Peripheral coronary pressure (systolic mm Hg)	53 ± 4	87 ± 7†
(diastolic mm Hg)	18 ± 2	33 ± 4†
(mean mm Hg)	35 ± 3	56 ± 4†
Peripheral coronary flow (ml /min)	1 4 ± 0 2	3 5 ± 0 5†
Collateral resistance (arbitrary units)	81 ± 13	43 ± 7
Infarct blood flow (ml /100 Gm /min)	17 6 ± 2 7	39 6 ± 4 3†
Infarct resistance (arbitrary units)	2 2 ± 0 3	1 6 ± 0 2
Infarct oxygen consumption (ml /100 Gm /min)	2 8 ± 0 5	5 3 ± 0 8†

$P < 0\ 05$
†$P < 0\ 0005$

administration of noradrenaline precipitated irregularities of cardiac rhythm These consisted of nodal rhythms (6 experiments) or of bursts of ventricular ectopic activity (6 experiments) Reversion to sinus rhythm invariably occurred during the infusion period and in these animals it was possible to demonstrate that noradrenaline increased sinus activity and sometimes reduced ST segment depression In all except one experiment left circumflex flow was markedly elevated during the period of the infusion and there was a substantial increase in normal myocardial consumption (Table I) Noradrenaline did not change coronary sinus Po_2 (29 ± 1 to 30 ± 2 $P > 0\ 5$) or the oxygen extraction coefficient (52 ± 2 to 51 ± 3 per cent $P > 0\ 9$) The ratio of oxygen available to the normal myocardium (flow × arterial oxygen content) to oxygen consumed by the myocardium was unchanged

The hemodynamic effects of noradrenaline are illustrated in Fig 1

The effect of noradrenaline on blood pH and gas tensions A consistent and significant finding was a decrease in arterial pH during the noradrenaline infusion (7 439 ± 0 024 to 7 379 ± 0 023 units $P < 0\ 001$) This was reflected in similar changes in coronary sinus and coronary vein pH (coronary sinus 7 356 ± 0 023 to 7 322 ± 0 024 units $P < 0\ 001$ coronary vein 7 337 ± 0 025 to 7 313 ± 0 023 units $P < 0\ 01$) and was almost entirely due to a small but significant elevation in arterial Pco_2 (32 ± 2 to 35 ± 2 mm Hg $P < 0\ 01$) Arterial base deficit was not significantly altered by noradrenaline (−5 8 ± 1 7 to −8 2 ± 1 2 mEq /L $P > 0\ 01$) In our experience a base deficit of −5 mEq /L is normal in dogs anesthetized with trichloroethylene Calculation of the pulmonary shunt ratio by the method described by Hyde[18] indicated that noradrenaline increased shunting in this experimental preparation from a mean of 17 ± 2 per cent of the cardiac output to 24 ± 2 per cent This change was significant ($P < 0\ 001$) However arterial Po_2 was not significantly altered by noradrenaline (272 ± 23 mm Hg before and 194 ± 40 during the infusion $P > 0\ 1$) All the above changes were readily reversible within 10 to 20 minutes of stopping the infusion

The effects of noradrenaline in the ischemic myocardium Some of these results are summarized in Table II Noradrenaline markedly increased peripheral coronary pressure and there was some evidence that this directly resulted from the elevated systemic arterial pressure (Fig 2) Flow in the ischemic region as measured by ^{133}Xenon clearance (Fig 3) or by retrograde flow (PCF) was markedly increased in all except one of the twelve experiments The exception was the same animal in which there was no change in left circumflex flow in response to noradrenaline and it may be significant that this dog had an abnormally acid arterial pH of 7 290 units and base deficit of −16 mEq /L There were substantial increases in oxygen consumption by the ischemic myocardium during noradrenaline administration (Table II) but no change in either oxygen extraction

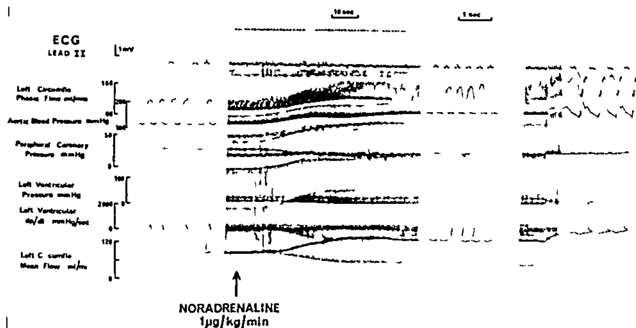


Fig. 1 The effects of an infusion of noradrenaline (1 0 µg/Kg /min commencing at the arrow) on (*from above*) the electrocardiogram (Lead II) left circumflex coronary blood flow (phasic ml /min) aortic pressure (mm Hg) peripheral coronary pressure (mm Hg) left ventricular pressure (mm Hg) and dP/dt (mm Hg $^{-1}$) mean circumflex flow (ml /min) in a dog whose left anterior descending coronary artery had been ligated 2½ hours previously The right hand portion of the trace was recorded towards the end of the 12 min infusion period

left ventricular end diastolic pressure (LVEDP) was significantly elevated (from 10 1 ± 1 6 to 16 ± 3 mm Hg) this unchanged LV dP/dt with an increased preload indicates a reduction in myocardial contractility This is presumably because of the functional loss of a considerable portion (25 to 30 per cent) of the left ventricular wall [15] The area supplied by the ligated vessel was cyanosed bulging and clearly non contractile and there was electrocardiographic evidence (ST segment depression) of myocardial ischemia Flow in this ischemic region was 17 6 ± 2 7 ml /100 Gm / min , which corresponds to a reduction of about 80 per cent of the flow in this area prior to ligation [7] In contrast there was no change in blood flow to the normal region of the left ventricular wall or in oxygen consumption by the normal myocardium The hemodynamic effects of acute coronary artery ligation are summarized in Table I

The marked changes in local venous blood draining an acutely ischemic region in this experimental model have been outlined by Fisher and colleagues [7] There is a substantial production of lactate a marked increase in Pco_2 and decreases in pH and oxygen content These changes are however transient and at the time that noradrenaline was administered (2 to 3 hr post ligation) there were again no differences in Po Pco_2 or pH between the coronary sinus blood (draining essentially normal areas of the myocardium) and coronary venous blood (draining the ischemic area) Before ligation the values for coronary venous blood were Po_2 31 ± 2 mm Hg Pco_2 44 ± 2 mm Hg pH 7 353 ± 0 014 units and the oxygen extraction coefficient 52 ± 3 per cent The corresponding values 2 to 3 hr after ligation were 27 ± 1 mm Hg 47 ± 3 mm Hg 7 337 ± 0 025 and 59 ± 3 per cent Comparable values for coronary sinus blood were Po_2 32 ± 2 mm Hg Pco_2 44 ± 2 pH 7 364 ± 0 014 units and the oxygen extraction coefficient 50 ± 3 per cent and 2 to 3 hr after ligation 29 ± 1 mm Hg 44 ± 3 mm Hg 7 356 ± 0 023 and 52 ± 2 per cent

Hemodynamic effects of noradrenaline When administered 2 to 3 hr after acute coronary artery ligation noradrenaline (1 0 µg per kilogram of body weight per minute) markedly elevated systemic arterial pressure cardiac work and LV dP/dt (Table I) In each of the twelve experiments the

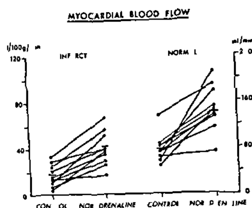


Fig 3 The effect of noradrenaline (1 0 μg/Kg /min) on blood flow (ml /min) in normal myocardium and in a region supplied by a ligated coronary artery (infarct blood flow ml /100 Gm /min)

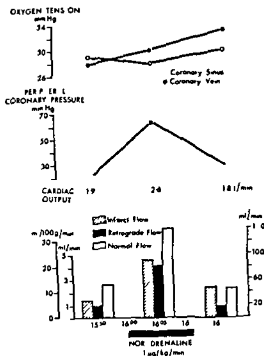


Fig 4 The effect of noradrenaline (1 0 μg/Kg /min) in a dog 2 to 3 hr after coronary artery ligation From above coronary sinus and vein Po_2 (mm Hg) mean peripheral coronary pressure (mm Hg) normal myocardial blood flow (□ ml /min) retrograde flow from the ligated vessel (■ ml /min) and flow within the ischemic region (infarct flow ▨ ml /100 Gm./min) The artery was ligated at 13[35] hr Noradrenaline (administered at time 16[00] hr to 16[15] hr) markedly elevated flow both in the ischemic region and in the essentially normal myocardium

preparations where PCP was only slightly elevated This would seem to indicate an active vasodilator mechanism *in* at *least* some of the experiments There is however no need to postulate a direct vasodilator action of noradrenaline in the ischemic myocardium Vasodilation is more likely to be due to the elevated perfusion pressure washing out metabolites from the ischemic muscle and this could account for the decreased vascular resistance in the infarct Noradrenaline certainly increased the carbon dioxide tension (from 47 ± 3 to 53 ± 3 $P < 0.02$) and decreased the pH (from 7 337 ± 0 02 to 7 313 ± 0 023 units $P < 0.01$) of blood draining the ischemic area We believe however that such active vasodilator changes are of minor importance The *major* factor increasing flow in the ischemic area is the elevated perfusion pressure This would be in agreement with the finding of Maroko and colleagues[6] that the extent of ischemia is highly dependent upon systemic blood pressure elevating systemic pressure (with methoxamine) decreased the extent of ischemic muscle injury while decreasing systemic pressure (by hemorrhage) increased both the area and the severity of ischemia

It has not been possible in this study to separate flow changes in the epicardial and endocardial regions of the ischemic area Partial coronary occlusion is accompanied by a disproportionate decrease in endocardial flow[18 20] and this is probably the explanation for the more extensive necrosis which occurs in subendocardial layers after coronary artery occlusion[21] Postmortem sectioning of the ischemic region showed clearly that this was also the case in the present experiments Fulton[22] has postulated that blood flow into the subendocardial plexus (supplying the inner layers of the myocardium) only occurs during diastole This means that the effective driving pressure for the endocardial region is the difference between the pressure in the coronary artery during diastole and the end diastolic pressure in the left ventricle This would normally be about 110 mm Hg (Table I) After coronary ligation however this is drastically reduced since it then becomes the difference between diastolic

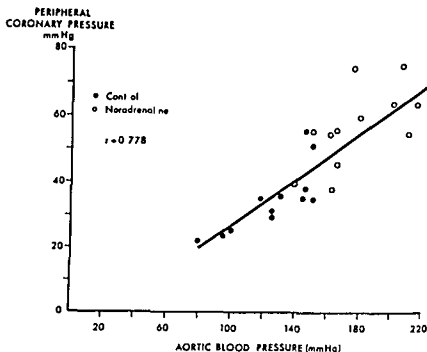


Fig 2 The relationship between systemic aortic blood pressure (mm Hg) and peripheral coronary pressure (mm Hg) before (●) and after (○) noradrenaline in dogs subjected to acute coronary artery ligation

(59 ± 3 per cent before noradrenaline and 51 ± 4 per cent during the infusion) or in coronary vein Po_2 (27 ± 1 mm Hg to 31 ± 3 mm Hg P > 0 05) The ratio of oxygen available to the ischemic area to oxygen consumed by the ischemic area was unchanged by noradrenaline

Some attempt was made to calculate vascular resistance changes both in the normal myocardium and in the ischemic region Vascular resistance in the normal myocardium was slightly (P < 0 02) reduced by noradrenaline This was so whether resistance was calculated from mean flow or from flow during diastole Resistance in the ischemic region was separated into 'collateral network resistance (the resistance to flow of the collateral vessels supplying the ischemic region) and "infarct resistance (the resistance of the smaller vessels of the ischemic region itself) Noradrenaline decreased resistance to flow both in the *infarct* and, more markedly in the collateral network (Table II) and increased the pressure gradient across the collateral network (mean systemic pressure —mean PCP) from 90 to 121 mm Hg [12] Some of the effects of noradrenaline on the ischemic myocardium are illustrated in Fig 4

Discussion

These results demonstrate that noradrenaline increases blood flow through a region of myocardium made ischemic by the ligation of a major branch of the left coronary artery Such an increase in flow could be due to the increased perfusion pressure (in this case the PCP) and/or to an active drug induced vasodilator mechanism In the normal myocardium it is generally agreed that with noradrenaline both mechanisms operate [17] There is both an increased perfusion pressure and also active vasodilation The latter is secondary to the raised myocardial oxygen consumption which results from increased contractility It is likely that both mechanisms also operate in the ischemic myocardium If the increase in nutritional blood flow (^{133}Xenon clearance) resulted solely from an elevated perfusion pressure one would expect a linear relationship between these variables In general when PCP is plotted against infarct blood flow (Fig 5) there is a good relationship There is however a greater scatter when the noradrenaline results are plotted on the same graph and, although over all the flow/perfusion pressure relationship was still linear, considerable increases in ^{133}Xenon clearance occurred in

external cardiac work and an increase in left ventricular *end-diastolic pressure* with an unchanged LV dP/dt This is indicative of reduced myocardial contractility Blood flow in the area supplied by the ligated vessel fell to a mean of *17 6 ± 2 7 ml/100* Gm/min which is about 20 per cent of the normal flow in this region

Infusing noradrenaline 2 to 3 hr after ligation increased systemic arterial pres sure LV dP/dt max external cardiac work and blood flow and oxygen consumption in normal areas of the myocardium There was some evidence that pulmonary shunt ing was increased by the drug

Noradrenaline also markedly increased peripheral coronary pressure and blood flow in the ischemic region as assessed by [133]Xenon clearance and by retrograde flow from the ligated vessel Oxygen consump tion in the ischemic region was also in creased by noradrenaline It is suggested that part of the increase in flow occurs in the endocardial region since the effective subendocardial perfusion pressure is in creased by noradrenaline This increase in flow would account for the reduction in infarct size which has been observed by other workers when the systemic arterial pressure is raised

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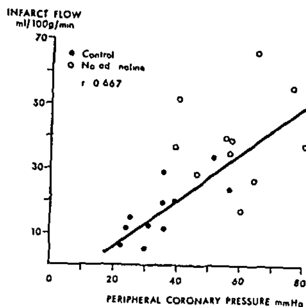


Fig 5 The relationship between infarct blood flow ([133]Xenon clearance ml/100 Gm/min) and peripheral coronary pressure (mm Hg) in nine dogs 2 to 3 hr after coronary artery ligation before (●) and during (O) the infusion of noradrenaline

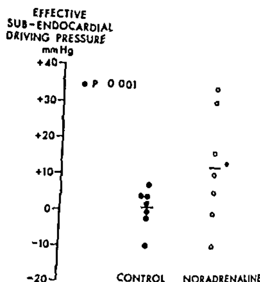


Fig 6 The effect of noradrenaline (1 0 μg/Kg/min) on the effective sub endocardial driving pressure (mm Hg calculated a diastolic PCP minus LVEDP see discussion) The control values are those for the ischemic region obtained immediately prior to the noradrenaline infusions

peripheral coronary pressure and LVEDP The left ventricular end diastolic pressure is as we have seen (Table I) elevated after ligation Such calculated effective sub endocardial driving pressures are shown in Fig 6 It can be concluded from these experiments that there is hardly any pressure head for flow in the inner (deep) muscle layers of the developing infarct Noradrenaline, however substantially increased the effective driving pressure (Fig 6) It is likely therefore that part of the increased flow which occurs through the total ischemic area during the administration of noradrenaline represents flow through the subendocardium Thus although there is no evidence that noradrenaline increases the ratio of LV endocardial flow to LV epicardial flow in the normal myocardium [18] these present results might suggest that like propranolol [20] the ratio of LV endocardial/LV epicardial flow is increased by noradrenaline in the ischemic myocardium An alternative way of increasing LV endocardial perfusion would be to reduce LVEDP This has been suggested as the possible mechanism through which the β adrenoceptor drug oxyfedrine increases flow in developing infarcts [23,24]

The finding that noradrenaline increases tissue perfusion in ischemic muscle would explain the finding, in patients in shock following acute myocardial infarction that myocardial lactate production is shifted to extraction during noradrenaline administration [5] It would also explain the finding that elevating systemic pressure is a factor which leads to a reduction in infarct size following experimental coronary artery occlusion in dogs [6] The fact that infarct oxygen consumption is increased by noradrenaline in our experiments suggests that within the infarcting myocardium there are viable as well as dead cells and that noradrenaline by restoring oxygen availability to these potentially viable cells reduces cell death and decreases the area of necrosis

Summary

The effects of infusions of noradrenaline (1 0 μg/Kg/min) were studied in dogs 2 to 3 hr after acute ligation of the anterior descending branch of the left coronary artery The model allowed blood flow to be simultaneously measured in the ischemic (infarcting) region and in the normal myocardium Sampling blood from a local vein (draining the ischemic region) and from the coronary sinus (draining the normal myocardium) allowed comparisons to be made of oxygen consumption by the two regions

Coronary artery ligation resulted in a marked decrease in car[illegible]tput ar

The effect of heroin and multiple drug abuse on the electrocardiogram

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Sudden death following parenteral injection of heroin is not a rare occurrence Although the term narcotic over dose has been used to describe the sudden death phenomenon it is now realized that in many instances the concentration of heroin in the tissues or blood is insufficient to cause toxicity and the precise mechanism of death is not clear[1]

It is not unreasonable that the sudden death syndrome seen in heroin users may be similar to those occurring in those with electrocardiographic abnormalities and are related to cardiac arrhythmias The following study was undertaken in an attempt to define the effects of street heroin and other drugs of abuse on the electrocardiogram

Materials and methods

Seventy five asymptomatic individuals admitted to a methadone maintenance treatment program (MMTP) served as the study group All patients received a complete history and physical examination including a chest x ray A 12-channel SMA (sequential multiple analyzer) was performed as well as serum analysis for sodium potassium chloride CO_2 content urea nitrogen and glucose Urine analysis with thin layer chromatography[2] was performed to detect the presence of morphine (heroin) methadone quinine barbiturates and amphetamines Routine and microscopic urine analysis was also performed Any individual with cardiac pulmonary or renal disease by either history physical examination or laboratory findings was excluded from the study A standard 12 lead ECG was obtained after a 20 minute rest period and was analyzed for abnormalities All QT intervals were corrected for heart rate according to the tables of Ashman and Hull[3]

Two groups of patients were studied Group I (34 patients) had electrocardiograms while on parenteral heroin prior to initiation of methadone therapy All gave a history of having used heroin confirmed by urine analysis within a 24 hour period of their ECG Serum was drawn for the appropriate laboratory studies upon completion of the ECG Group II comprised 41 patients who had been on methadone maintenance for varying periods of time but were still using other drugs sporadically notably alcohol barbiturates heroin or cocaine All of these patients were found to have barbiturates in their urine or gave

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Table IV *Correlation of heart rate QT interval and urine analysis (Group I patients)*

Patient no and initials	Heart rate	QT	QT	Urine analysis				
				Morphine	Methadone	Barbiturate	Amphetamine	Quinine
1 C A	102	40	↑	0	+	0	0	+
2 C. J	70	42	↑	+	+	0	0	0
3 H S	75	38		+	+	0	0	0
4 H D	60	43		+	0	0	0	+
5 I N	65	38		+	0	0	0	0
6 I J	65	38		+	+	0	0	0
7 J A	104	—		+	0	0	0	+
8 I S	60	36		+	0	0	0	0
9 M L	75	37		0	0	0	0	0
10 R F	48	40		+	0	0	0	+
11 R. J	85	38		+	0	0	0	0
12 R. H	50	40		+	+	0	0	0
13 S J	100	32		+	0	0	0	0
14 S P	75	36		+	+	0	0	+
15 S C	110	30		0	+	0	0	0
16 T O	75	40	↑	+	+	0	0	0
17 V A	[illegible]0	38		0	+	0	0	0
18 V P	98	32		0	0	0	0	0
19 V D	78	36		0	0	0	0	0
20 S G	71	36		+	0	0	0	0
21 A M	68	37		+	+	0	0	0
22 B J	62	39		+	0	0	0	0
23 D L	93	40	↑	+	0	0	0	0
24 C N	68	37		+	0	0	0	+
25 M M	[illegible]0	38		+	+	0	0	+
26 O P	58	37		+	0	0	0	0
27 P D	52	42		0	+	0	0	0
28 R R	70	41	↑	0	+	0	0	0
29 R. D	72	38		0	0	0	0	0
30 R S	85	36		+	0	0	0	+
31 S V	62	40		0	+	0	0	0
32 S F	58	36		+	+	0	0	0
33 T R.	57	36		+	+	0	0	+
34 W A	64	42	↑	0	+	0	0	0

*C rrected QT int rvals fo rat that are ncreased as per Ashman and H ll[8]

postmortem were negative for all abusive drugs[1]

The precise mechanism of death is not clear Those postulated include a pharmacologic overdose an allergic type reaction to heroin acute reactions to injected bacteria quinine or other foreign material anoxia synergistic effects from multiple drug abuse and pulmonary edema.[5, 7] Pulmonary edema in patients with acute intoxication has been recognized for nearly a hundred years[8] though its pathogenesis remains obscure

The sudden onset and rapid fatal termination of the acute reaction with the needle found remaining in the vein in some instances[1] allows for the possibility of a fatal arrhythmia being the mode of exodus in these patients

Heroin is three to four times more potent than morphine and when injected is hydrolized rapidly to monoacetyl morphine and subsequently to morphine It is excreted in the urine largely as free and conjugated morphine Morphine and related narcotics act by increasing vagal tone and by inhibiting the hydrolysis of acetylcholine[9] The effect of morphine on heart

Table I Age distribution of patients

Age	Group I	Group II
10-19	0	0
20-29	18	15
30-39	13	19
40-49	3	6
50-59	0	1
F/M*	7/27	9/32

*Female male ratio

Table II Cardiac abnormalities in patients in Group I

Cardiac abnormality	No
Bradyarrhythmia	6
QT prolongation	6
Sinus tachycardia	2
Intra atrial conduction disturbance	2
Abnormal T waves	2

Table III ECG changes in 15 patients taking heroin within 4 hours of examination (Group I)

Abnormality	No
Tachycardia or bradycardia	7
Increased QT	2

a history of drug abuse within a three day period of their electrocardiogram

The ECG s of 32 patients (Group III) free of cardiac pulmonary or renal disease matched for age and ethnic background were obtained from a routine employee health screening clinic These individuals did not have a history of drug abuse

Results

There were no serum or routine urine abnormalities in any group The age distribution of patients is shown in Table I The average age of Group I was 30 years Group II, 33 years and Group III 34 years The female/male ratio was approximately 1 to 4 in each group

Of the 34 patients in Group I (only on heroin) abnormalities of the electrocardiogram were noted in 19 patients (55 per cent) (Table II) Of 15 patients who had taken heroin within 4 hours of their ECG changes were noted in 10 (68 per cent) (Table III) The most frequent abnormality in this group was a prolonged QT_c interval (19 per cent) and bradyarrhythmias (sinus arrhythmias with slow ventricular response or sinus bradycardia) (19 per cent) Correlation of heart rate, QT interval and urine analysis in Group I patients is seen in Table IV Of the 41 patients on methadone with a history of multiple drug abuse Group II, 27 (66 per cent) had some ECG changes QT_c prolongation was noted in 14 (34 per cent) prominent U waves in 13 (32 per cent) and bradyarrhythmias in 13 (32 per cent) (Table V) The most striking electrocardiogram in this group is from a 31 year-old addict of 17 years duration who died suddenly on the street He was on 100 mg of methadone a day and had an impressive barbiturate habit as well as a history of sporadic parenteral cocaine use The ECG (Fig 1) taken several days prior to his death revealed marked prolongation of the QT_c interval 0 48 sec with U waves of greater amplitude than the T waves Postmortem examination by the medical examiner s office revealed a fresh puncture site but no gross abnormalities of the heart or lungs Subsequent toxicological reports were negative except for the presence of methadone

In the control group sinus bradycardia was present in 4 patients (12 5 per cent) and none had QT prolongation

Discussion

Mortality rate related to heroin addiction has been increasing steadily In New York City it was reported that narcotics chiefly heroin were the leading cause of death in 1969 and in 1970 in all males aged 15 to 35 including non addicts [4] An acute drug reaction was the cause of death in more than three quarters of all fatalities from narcotics however a pharmacologic lethal level could not be demonstrated in most cases In some toxicological studies at

Table V Cardiac abnormalities in patients in Group II

Cardiac abnormality	No
QT prolongation	14
Prominent U wave	13
Bradyarrhythmias	13
Dimpled T wave	7
Abnormal T wave (Low voltage inversion peaked)	5
Abnormal LAD	2
First degree heart block	2
Intra atrial conduction abnormality	2
Premature systoles (apc s vpc s)	3
Tachycardia	1

Table VI ECG changes in drug abuse

	No of patients	*Abnormal ECG*	*QT increased*	*Brady arrhythmias*
Group I	34	19	6	6
Group II	41	27	14	13
Group III	32	—	—	4

In our series of patients transient atrial fibrillation was not found However brady arrhythmias and repolarization abnormalities were common in both groups (Table VI) Bradycardia enchances ventricular ectopic activity lowers the threshold to ventricular fibrillation [20 21] and may serve as an important factor in precipitating ventricular tachycardia fibrillation and sudden death

Prolongation of the QT interval represents delayed ventricular repolarization and an increase in the duration of the vulnerable period with greater susceptibility to the development of a ventricular dysrhythmia In the presence of the QT prolongation single or multiple ventricular premature beats may lead to ventricular fibrillation and death In addition it has been found that excitement and fright usually cause the QT interval to prolong further [22] In the addict usually operating under severe stressful situations additional lengthening of an already prolonged QT interval may well be responsible for ventricular fibrillation and death

In these individuals with multiple drug abuse the hypotension produced by barbiturates [2] respiratory depression produced by methadone [24] and the increased incidence of ventricular arrhythmias associated with alcohol [25] when superimposed on underlying repolarization abnormalities may precipitate lethal arrhythmias

The setting under which sudden death occurs in narcotic abusers is not amenable to monitoring and therefore to provide electrophysiological evidence for the role of ventricular arrhythmias in the acute fatal reactions is not possible However the existence of an impressive number of repolarization abnormalities and brady arrhythmias in asymptomatic users of heroin and other abusive drugs makes the possibility of fatal arrhythmias real

The essential problem revolves around the identification of the subject prone to sudden death At present longitudinal studies are under way in patients maintained on methadone who are free of other abusive drugs to determine if the initial electrocardiographic abnormalities can revert to normal with time

Summary

The electrocardiograms (ECG) of 75 asymptomatic individuals admitted to a methadone treatment program were analyzed to determine the effect of street heroin and other drugs of abuse All patients were free of cardiac renal or pulmonary disease and had no laboratory abnormalities Two groups of patients were studied In Group I there were 34 patients on heroin only which was taken within 24 hours of the ECG Abnormalities were noted in 55 per cent QT prolongation was found in 19 per cent and significant bradyarrhythmias were found in 19 per cent In Group II there were 41 patients on methadone with multiple drug abuse changes were found in 66 per cent QT prolongation was noted in 34 per cent prominent U waves in 32 per cent and bradyarrhythmias were found in 32 per cent

It is now a well known fact that the sudden death syndrome in addicts may not be a pharmacologic or dosage related phenomenon The existence of conduction depolarization and repolarization abnor

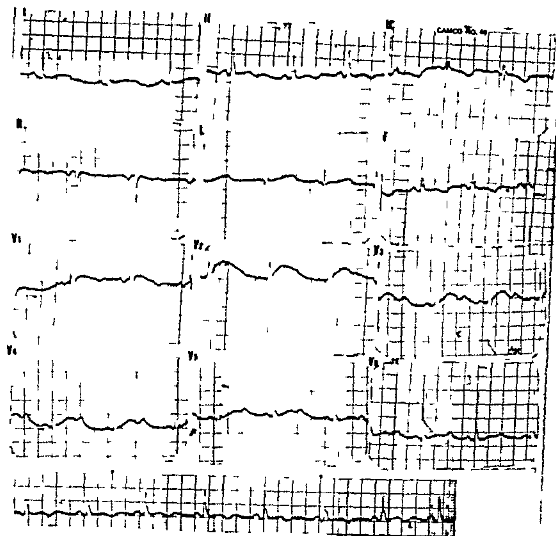


Fig. 1. ECG of a 31 year old male drug addict who died suddenly. The QT_c was 0.48 sec. and the U wave was prominent.

rate has been found to be variable. Keats and colleagues[10] stressed the tremendous individual variation in response to narcotics and noted variable severity of different side actions in single subjects. Morphine in man has been found by some to slow the heart rate,[11,12] some found an increase,[13,14] and others showed no change.[15] Our findings of bradycardia and tachycardia in a significant proportion of Group I and Group II patients may be related to the variable response to morphine or to yet other related factors or drugs.

Quinine, often used as a diluent in illicit heroin preparations, alters the ECG in the same manner as quinidine; however, a greater dose is required to produce the same effect.[16] Low doses may increase the sinus rate but higher doses produce sinus bradycardia. Its toxic effect may be dose dependent or dose independent. The rhythm disturbances resulting from quinidine most likely are secondary to a reentrant mechanism promoted by QT_c prolongation and slow conduction[16] and possibly by an increased dispersion of the refractory period.[17]

ECG abnormalities secondary to heroin addiction have been infrequently reported in the literature. Atrial fibrillation has been reported by some.[18,19] Labi[18] was first to describe paroxysmal atrial fibrillation secondary to heroin intoxication in six patients. In four of these cases, rapid atrial fibrillation with a slow ventricular response was documented prior to therapy with nalorphine hydrochloride. Reversion to regular sinus rhythm after a phase of coarse atrial fibrillation with rapid ventricular response occurred in five. Anoxia and increased vagal tone caused by the drug was postulated as the etiologic mechanism.

Encephalomyocarditis (EMC) virus infection of the mouse aorta*

An ultrastructural study

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The encephalomyocarditis (EMC) virus was first recovered in 1945 from anthropoid apes[1] and later in 1957 from Aotus monkeys.[2] Since then, three fatal outbreaks of myocarditis in domestic swine have been attributed to the EMC virus.[3,4] There are no reports of EMC viral myocarditis in man. However, Koch[5] isolated the virus from earwashings, feces, blood, and cerebrospinal fluid of three patients. A serosurvey of the human populations of southern Louisiana and Peruvian Indians[6] showed positive neutralizing antibodies to EMC virus in high titer.

In this laboratory, EMC virus has been shown to produce myocarditis,[7,8] valvulitis,[9] mural and valvular endocarditis,[10] as well as nephritis,[11] pancreatitis,[12] and hepatitis[13] in experimental animals. This report describes the electron microscopic findings in the aortas of mice infected with EMC virus.

Materials and methods

EMC virus stock was originally obtained from Glasgow.[14] The virus was prepared by three passages in mouse cardiac cells and 3 passages in L-cells. The titer of the cultivated virus fluid was determined to be 10^{6} $TCID_{50}$. Culture fluid free of virus was used as a control inoculum. Ten one- to two-day-old Swiss mice were inoculated intraperitoneally with 0.025 ml. of the EMC virus culture fluid and were killed one day later. Two mice were used as controls.

The mice were killed by cervical fracture and the internal organs were quickly removed to expose the aorta. The aorta was bathed *in situ* for 5 minutes with 3 per cent phosphate buffered glutaraldehyde and was then excised and placed in fresh glutaraldehyde for 2 hours. After a 2- to 3-hour phosphate buffer rinse, the aorta was postfixed in 1 per cent phosphate buffered osmium tetroxide for 1.5 hours. Dehydration was accomplished in methanol with final embedment in epoxy resin. Thin sections were cut with a Porter Blum MT 2 ultramicrotome or an LKB Ultratome. Sections were stained with 1 per cent aqueous uranyl acetate and lead citrate and

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malities, as well as bradyarrhythmias in a significant number of drug dependent individuals may play a role in the production and facilitation of lethal arrhythmias and may be the mechanism of the acute fatal reaction

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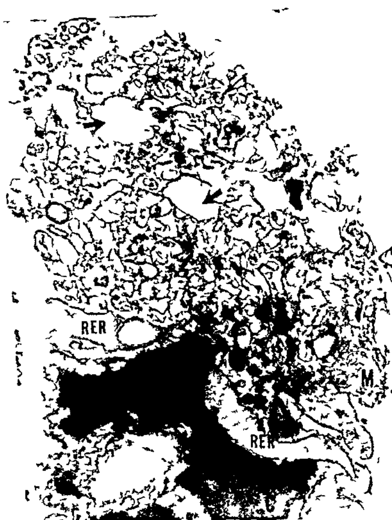


Fig 2 Adventitial cell of aorta from EMC irus infected newborn mouse showing extensive necrosis The cytoplasm is filled with membrane-bound vesicles (*small arrows*) and vacuoles (*large arrows*) Fragmented profiles of rough endoplasmic reticulum (*RER*) show dilatation and accumulation of dense material within the cisternae The nuclear chromatin (*C*) is condensed Occasional mitochondria (*M*) are dilated (Original magnification X31 00)

age consisted of slight to extensive vesiculation and vacuolization of cytoplasmic membrane systems dilatation of rough endoplasmic reticulum and accumulation of electron dense material within the cisternae (Fig 2) Often the nuclear chromatin was condensed Viral crystals were frequently encountered in association with the intracellular necrosis (Figs 3 4 and 5)

Occasionally the smooth muscle cells in closest proximity to the adventitial tunic were damaged The necrosis within smooth muscle cells was identical to that observed in fibroblasts (Figs 4 and 5) Viral crystals also were found in association with the intracellular necrosis in cells which could clearly be identified as smooth muscle cells (Figs 4 and 5)

Viral crystals were found in the aortas of all 10 animals studied The crystals were composed of dense particles arranged into a cubic configuration (Figs 3 and 4) Viral crystals were located in adventitial fibroblasts and medial smooth muscle cells within fragments of unidentifiable cells



Fig. 1. Low magnification electron micrograph of an apparently unaffected portion of aorta (cut in cross section) from ECM viral inoculated newborn mouse. An endothelial cell (*E*) lining the lumen (*L*) is immediately bordered by a band of elastic fibers (F_1). Other bands of elastin (F_2 to F_7) alternate with smooth muscle cells (*SM*) of the media. The adventitial layer (*A*) is adjacent to F_7. Cellular components of the adventitia are not clearly demonstrated in this micrograph. A part of a leukocyte (*arrow*) is visible in the adventitia. (Original magnification ×6,900.)

were examined with a Siemens Elmiskop I electron microscope.

Results

The newborn mouse aorta was roughly separable into three layers (Fig. 1). The intima was a single layer of flattened endothelial cells which had an enlarged nucleus that protruded into the aortic lumen. There was no cellular subendothelial layer. The medial tunic was the thickest layer, being composed of several layers of smooth muscle cells separated by bands of elastic fibers (Fig. 1). Subjacent to the media was a loosely constructed adventitia, consisting mostly of fibroblastic cells and loose collagen bundles. Occasional blood cells of undetermined types were encountered which possibly had infiltrated into the adventitia.

Cells exhibiting necrosis in the infected animals were found most frequently within the adventitia. These cells were severely damaged and frequently only fragments of cells were found; thus it was difficult to determine the cell types accurately. Dam



Fig 4 EMC viral infected smooth muscle cell of the media of newborn mouse aorta A small perinuclear area of intracellular necrosis (*top arrow*) contains a viral crystal (*V*) A similar area of necrosis (*bottom arrow*) is close to the nucleus (*N*) The smooth muscle cell is bordered on both sides by elastic fibers (*F*) (Original magnification ×19 800)

and eventually initiate cellular necrosis and aortitis or arteritis which may later develop into scarring of the aorta or arteries If the vasa vasorum is infected an endarteritis such as is found with syphilis may occur and medial necrosis or inflammation may ensue Such possibilities need further investigation

Histologically there has been no vasa vasorum found to penetrate the media of mouse aorta The structure of the aorta of mouse may be different from that of man In this study fibroblasts were not found in the intima and media of mouse aorta This may have been due to the fact that the mice were killed only a short time after viral inoculation limiting the extent of the disease process To find a virus injured fibroblastic cell in intima or media after such a short interval of infection may be difficult but it is possible that such cells would be found with advancement of the disease That the EMC virus can infect fibroblasts of mice is true as discussed above We suggest that this virus or some other viruses can infect fibroblasts in man



Fig. 3. Adventitial cell of aorta from EMC virus infected newborn mouse. An area of intracellular necrosis (*arrow*) characterized by membrane bound vesicles and vacuolization is in intimate association with an EMC viral crystal (*V*). Mitochondria (*M*) are not swollen. (Original magnification ×45 000.)

in the adventitia and free within the extracellular spaces of the adventitia. No viral crystals were found within endothelial cells or within blood cells which were infiltrated into the adventitia.

The aortas of the two control mice were normal.

Discussion

There was direct infection of the adventitial and adjacent smooth muscle layers of the aorta by the EMC virus based on the finding of viral crystals and pathologic changes in the cells of these layers. The crystals had the same appearance as those previously demonstrated in the myocardium,[7] heart valves,[10] and kidney[11] of infected mice.

Clinically, there are reports of idiopathic medial aortopathy and arteriopathy[15] and nonsyphilitic aortitis[16] in man without a definite etiology or pathogenesis detected. Histologically, fibroblasts are present in all three layers of the aorta of man and the adventitial layer of the vasa vasorum, the small nutritional artery of the aorta.[17] Since the EMC virus is highly infectious to fibroblasts in mice, it probably can also attack the fibroblasts in the human aorta as well as vasa vasorum or other arteries

cells of the media in some of the animals The relationship of these findings to the production of aortitis or arteritis which could also ultimately result in arterio sclerosis is discussed

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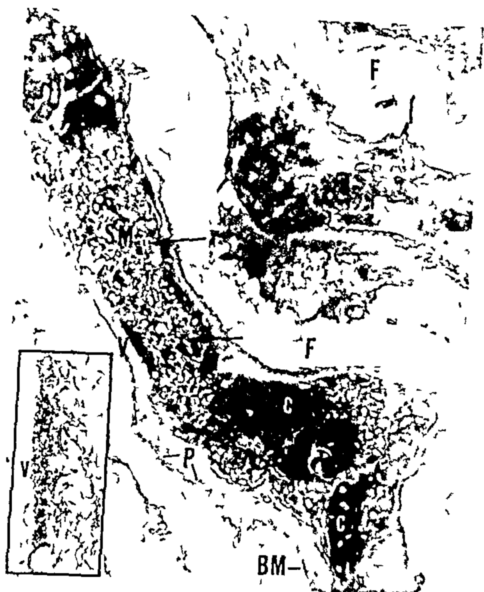


Fig 5 Portions of several smooth muscle cells of the media of a newborn mouse aorta 24 hours following inoculation with EMC viral culture fluid The *central portion* of one smooth muscle cell (*SM*) was filled with densely packed vesicles (*arrows*) An obliquely sectioned viral crystal (*V*) (*see insert*) is present on the outer border of the area of intracellular necrosis The nuclear chromatin (*C*) is condensed Separating the smooth muscle cell layers are elastic fibers (*F*) Pinocytotic vesicles (*P*) and an incomplete basement membrane (*BM*) support the identity of this cell as a smooth muscle cell (Original magnification ×9 800 insert magnified ×34 000)

possibly playing a role in the pathogenesis of clinical aortitis or arteritis which could ultimately result in arteriosclerosis Viral infection of medial smooth muscle cells is evidence that the media can become directly involved in the disease process in addition to being indirectly involved as a result of infiltration of cells which are susceptible to viral infection Furthermore intimal involvement could result from migration of virus injured smooth muscle cells or fibroblasts through fenestrae of the internal elastic lamina The significance of the aortic damage in relation to scarring and arteriosclerotic aortic disease remains unknown but deserves investigation

Summary

Electron microscopic findings in the aortas of 10 mice infected with encephalomyocarditis (EMC) virus are described Cellular necrosis was found mostly in the adventitia and occasionally in the smooth muscle cells closest to the adventitial tunic Viral crystals were frequently found in association with the intracellular necrosis Viral crystals were found in the adventitia of all 10 mice and in the smooth muscle

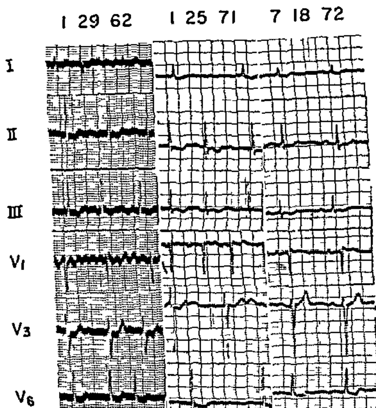


Fig *1* Serial electrocardiogram of Case No 1 patient H P (No 47 14069)

adequate mitral commissurotomy and it has been maintained for one year

Case 2 L G a Caucasian woman developed rheumatic fever at age 5 years A heart murmur was noted at age 29 and digitoxin 0 1 mg daily was started Later he developed bronchial asthma and the cardiac functional tate gradually declined Atrial fibrillation developed at age 47 when she wa first seen at the University Hospitals In addition to bronchial asthma she had a mitral facies a precordial lift cardiomegaly and the murmurs of mitral stenosis and mild mitral and aortic insufficiency The electrocardiogram showed atrial fibrillation with fibrillatory waves 3 mm in amplitude in Lead V A closed mitral commissurotomy was done in the same year with temporary improvement in the cardiac functional state Diuretic therapy was added to digitalis at age 53 but wheezing and dyspnea became almost constant requiring her to sleep on four pillows At age 56 prednisone therapy was begun which afforded her considerable relief from the asthma Coarse atrial fibrillat on was noted on every re-examination for 16 consecutive visits until age 59 when it was found that sinus rhythm had returned spontaneously The electrocardiogram at this time showed right ventricular hypertrophy left atrial disease short runs of atrial tachycardia with ging p axis and 1st degree A V block (Fig 2)

At age 60 diabetes mellitus was discovered She was last seen in 1972 at age 61 and had isorhythmic A V dissociation with a sinus mechanism and her major problem then was osteoporosis Atrial fibrillation which had persisted for a total of twelve years after an adequate mitral commissurotomy converted spontaneously to sinus rhythm which has been maintained for the last two years

Case 3 A C a Caucasian woman had acute arthritis at age 8 and 15 years and at age 24 a cardiac murmur was noted At age 55 an electrocardiogram showed sinus rhythm with frequent premature atrial contractions During the following five years she experienced frequent paroxysms of a tachyarrhythmia recurrent lung infections with dyspnea and mild blood streaking of the sputum and gradual reduction in exercise tolerance Nocturnal dyspnea pulmonary congestion and atrial fibrillation appeared at age 60 during a severe respiratory infection Examination revealed a mitral facies right ventricular lift loud S_1 and P_2 and a long diastolic apical rumble Quinidine therapy restored sinus rhythm She had a closed mitral commissurotomy in the same year (age 60) and atrial fibrillation recurred twice within two weeks and once in the following year Digitalis and quinidine restored sinus rhythm each time Quinidine had to be stopped at age 62 because of cinchonism and coarse

Case reports

Spontaneous return of sinus rhythm in older patients with chronic atrial fibrillation and rheumatic mitral valve disease

Description of three patients

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Atrial fibrillation is a complication of rheumatic mitral disease probably determined less by the severity of the valve lesion than by the age of the patient [1,2] The majority of patients with mitral valve dis ease eventually develop atrial fibrillation coincident with clinical deterioration [3] and often it may be paroxysmal initially before it becomes the established rhythm [4] Once established for a few years, attempts at cardioversion may either fail to restore sinus rhythm[5,6] or if successful, sinus rhythm rarely is maintained for more than a few weeks or months [7-12]

That patients with mitral valve disease who have had atrial fibrillation for many years, occasionally may revert sponta neously to sinus rhythm and maintain that rhythm has not been previously empha sized One of the authors (L E J) has personally followed 120 patients for up to twenty years after closed commissurotomy Three of these patients spontaneously re verted to sinus rhythm after having atrial fibrillation for over ten years, they are the subject for this report

Case reports

Case 1 H P a Caucasian woman developed pneumonia at age 18 years when a heart murmur was first detected Pneumonia recurred with her first pregnancy three years later At age 31 she was seen at the University Hospitals with dyspnea coughing and wheezing and the findings of a right ventricular systolic lift loud S_1 and an apical diastolic rumble Chest x ray showed pulmonary venous congestion and a prominent left atrium and right ventricle Pneumonia recurred at age 34 and the following year she developed congestive heart failure during treatment for leg burns Digitalis and diuretics were given and later discontinued after five months Atrial fibrillation developed at age 36 accompanied by an increase in pulmonary congestion Digitalis improved her symptoms but dyspnea on mild exer tion and atrial fibrillation continued A closed mitral commissurotomy was performed at age 37 and a left atrial appendage thrombus was removed She developed an expressive aphasia which subse quently cleared Dyspnea improved and only mini mal mitral insufficiency was noted Atrial fibrillation was found on eight subsequent yearly visits Initially the fibrillation waves were 2 to 3 mm in amplitude in Lead V_1 but at age 47 they became 1 mm in amplitude in the same lead (Fig 1) Sinus rhythm with first degree A V block spontaneously returned at age 47 and has been maintained until the present time Sinus rhythm returned 12 years following the onset of atrial fibrillation and 10 years after an

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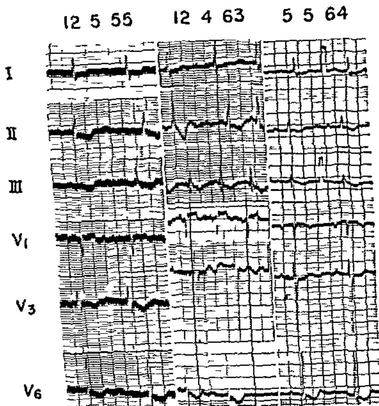


Fig 3 Serial electrocardiogram of Case No 3 patient A C (No 53-13783)

cardioverted or sinus rhythm was recovered only transiently Twenty two of 25 patients described by Semer and associates[7] with more than five years atrial fibrillation did not maintain sinus rhythm for six months following electroversion Similarly no patient with atrial fibrillation of more than five years *maintained* sinus rhythm for one year following cardioversion in the series reported by Radford and associates [8] Bailey and colleagues [9] Olesen and co workers [10] *or Upton and Honey* [11] *In our three patients* with atrial fibrillation for more than ten years one would have expected that attempts at defibrillation either would have *failed or if successful* that sinus rhythm could not be maintained Instead sinus rhythm spontaneously returned

In patients with rheumatic heart disease *established* atrial fibrillation has been correlated with pathologic changes in the atrial wall [9,16] and particularly with the extent of disease of the sinoatrial node and internodal pathways [18,20] Moreover there is recent evidence suggesting that the persistence of atrial fibrillation accentuates pathologic damage of the left atrium probably through dilatation and increased wall tension [20] This is generally thought to further decrease the chances of recovery of sinus rhythm On the other hand Holzmann[19] described one case of atrial fibrillation with spontaneous reconversion to sinus rhythm in whom the left atrium was found at autopsy to be converted into a fibrous sac The author suggested that initially the atrial fibrillation was triggered *by left atrial involvement and reconversion* occurred when all of the left atrial myocardium was destroyed

Recent atrial fibrillation usually shows *coarse f waves in the electrocardiogram*[21] but fibrillation waves become finer with chronicity[22] and with digitalis treatment.[23] Low amplitude f waves in the electrocardiogram generally are regarded as an unfavorable sign when defibrillation is to be considered [8] It is remarkable that the three patients included in this report maintained the coarse fibrillatory waves throughout the years and in spite of digitalis therapy a finding that may have been

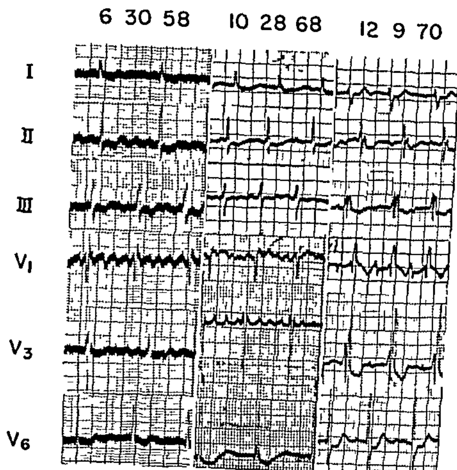


Fig 2 Serial electrocardiogram of Case No 2 patient L G (No 58 11748)

atrial fibrillation became the established heart rhythm noted on all subsequent visits for the next eight years She developed an anterior myocardial infarction at age 67 At age 70 intermittent atrial flutter was noted on one electrocardiogram (Fig 3) Sinus rhythm spontaneously appeared at age 71 with 1st degree A V block Digoxin had been her only medication for years She developed heart failure at age 74 and a cerebral vascular stroke at age 75 causing her death while still in sinus rhythm Thus this patient had atrial fibrillation which was recurrent for two years and established for nine years It spontaneously reverted to sinus rhythm eleven years after a closed mitral commissurotomy and the normal rhythm persisted for four years thereafter

Discussion

We have described three patients representative of a rarely recognized phenomenon[13 14] that is difficult to explain from our present knowledge of the pathogenesis and course of atrial fibrillation in rheumatic heart disease It is possible, however that this phenomenon is not this rare, and many more cases will be recognized when adequately looked for

Soon after successful mitral valve surgery, patients with atrial fibrillation may return to sinus rhythm occasionally spontaneously but more commonly with therapeutic defibrillation[6 12] Successful surgery may enhance the resumption of sinus rhythm, probably as a result of atrial decompression[15] It is conceivable that in our three patients the favorable effects of surgery may have allowed significant sustained reduction in left atrial pressure and wall tension with subsequent recovery of the sinus rhythm after more than ten years This assumption is however challenged by the observation that such reversion may still occur when there is almost total damage of the left atrium as determined pathologically[13]

It has been shown that the duration of atrial fibrillation is the most important single determinant of the immediate success and long term maintenance of sinus rhythm following cardioversion in patients with rheumatic mitral disease In the series reported by Lown,[6] 12 of 18 patients with atrial fibrillation of more than ten years duration either could not be electrically

Mitral disc variance (Harken prosthesis)

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Although the operative mortality and morbidity rate in surgical replacement of cardiac valves has decreased considerably in the past decade the development of mechanical dysfunction of prosthetic valves continues to be a serious problem Variance with ball valve prostheses in both aortic and mitral positions is well documented[1, 8] Low profile discoid valve prostheses have been used with increasing frequency for mitral valve replacement because of certain apparent advantages they have over ball valve prostheses in this position being light in weight having less inertia and having a short cage which occupies less space in the ventricle[8, 11] Nevertheless malfunction of various types of these disc prostheses has also been reported[9, 11, 22] We report the first such variance in a Harken Surgitool Discoid mitral valve prosthesis and discuss some of the unique features of disc variance of the mitral valve

Case report

Patient A N a 31 year old housewife with a history of rheumatic fever in childhood had been asymptomatic until April 1968 when during her fourth month of pregnancy she developed severe exertional and paroxysmal nocturnal dysprea and orthopnea. She was hospitalized in acute pulmonary edema and was found to have rheumatic heart disease with mitral stenosis and aortic regurgitation (N Y H A Class IV) She was treated with digitalis and diuretics and improved Subsequently she delivered a full term infant without further difficulty Over the next 1½ years she developed progressive exertional dyspnea. In June 1970 she was readmitted for cardiac catheterization because of limiting symptoms (N Y H A Class III) Severe mitral stenosis (calculated mitral valve area 0 9 cm^2) and minimal aortic regurgitation were demonstrated (Table I) Mitral valve replacement with a small (S/M 432 H) Harken Mitral Discoid valve prosthesis Magovern series (turtle neck) was performed on June 11 1970 Her postoperative course was uneventful and she returned to work as a nurse s aide She continued to take digoxin warfarin and prophylactic penicillin and was asymptomatic until 23 months after surgery when symptoms of palpitation progressive dyspnea orthopnea and paroxysmal nocturnal dyspnea suddenly reappeared After 10 days he sought medical attention and was hospitalized on May 4 1972 There was no history of fever hemoptysis or chest pain On examination her pulse was 100 per minute and regular Blood pressure was 96/48 mm Hg The jugular venous pressure was not elevated Basilar rales were present bilaterally The apical impulse was displaced slightly to the left and a right ventricular lift was palpable An intermittent Grade III/VI pansystolic murmur radiating toward the axilla and a Grade II/VI mid-diastolic

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relevant to their subsequent spontaneous reversion to sinus rhythm

It is interesting to note that with return of sinus rhythm the electrocardiograms consistently showed impaired atrioventricular conduction, a phenomenon that has been previously noted with therapeutic cardioversion of atrial fibrillation[24] It is also notable that with return of sinus rhythm there was practically no change in the clinical state or the digitalis require ments in any of these patients

With modern treatment and particu larly with improvement of surgical tech niques many more patients with rheumatic mitral disease may survive until old age Perhaps return of sinus rhythm after many years of established atrial fibrillation may not be too uncommon in such patients Further observation should determine the frequency of this phenomenon

Summary

Three patients with rheumatic mitral stenosis had had atrial fibrillation for over ten years before spontaneously restoring normal sinus rhythm Each had undergone a closed mitral commissurotomy ten to twelve years before the conversion Their ages at the time of resuming normal rhythm were 47, 59, and 71 years This unusual phenomenon has no satisfactory explana tion by our present knowledge of the natural history of mitral valve disease and the pathogenesis of atrial fibrillation

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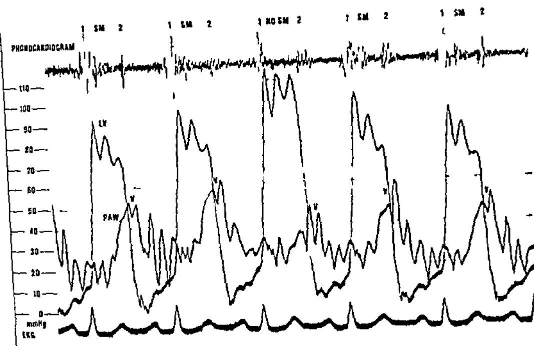


Fig 2 Simultaneous phonocardiographic (at the apex) left ventricular pressure pulmonary artery wedge pressure and electrocardiographic tracings Note that left ventricular systolic pressure and PA wedge V wave are variable from beat to beat The third cycle shows better valve function with lower V wave higher L V systolic pressure and absence of systolic murmur of mitral regurgitation *L V* = left ventricular pressure *PAW* = pulmonary artery wedge pressure *SM* = systolic murmur *V* = V wave of PAW

Table I Serial hemodynamic data

	6 3 70		5 5 72
	Resting	Exercise	Resting
Right atrium	3 mm Hg		7 mm Hg
Right ventricle	46/7 mm Hg		55/8 mm Hg
Pulmonary artery	46/22(30) mm Hg	100/58(75) mm Hg	55/26(42) mm Hg
Pulmonary artery wedge	(23) mm Hg	(60) mm Hg	(35) mm Hg
Left ventricle	100/4 mm Hg	135/0 mm Hg	100/16 mm Hg
Mitral valve gradient	26 mm Hg	59 mm	18 mm Hg
Calculated mitral valve area	0 9 cm^2	1 1 cm.^{2}	1 1 cm^2
Cardiac index	3 0 L/min/M^2	5 1 L/min/M^2	2 4 L/min/M^2

the mitral valve because of several apparent theoretical disadvantages inherent with the ball valve prosthesis in this position[1 3 9] These include protrusion of bulky valve structure into the left ventricular outflow tract contributing to low cardiac output arrhythmias due to impingement on the interventricular septum partial obstruction to blood flow by restricted orifice size and relatively slow response of the ball due to static inertia Matloff and colleagues[21 31] reported striking hemodynamic improvement and fall in pulmonary vascular resistance in the early postoperative periods in patients with Harken Discoid mitral prostheses Nevertheless both the complications of thrombosis and variance have been reported with mitral disc prostheses as well and can be responsible for serious congestive heart failure[9 12 22]



Fig 1, *A* through *C* Frames from 70 mm fluoroscopic spot films *A* abnormal wear of the superior edge of the disc is seen *B* and *C* worn disc is seen *incompletely* covering the inflow orifice (*B*) and projecting into the left atrium (*C*)

murmur at the apex and an early *decrescendo* Grade II/VI diastolic murmur in the left parasternal region were heard The opening and closing disc sounds varied in intensity from beat to beat At times the opening click was inaudible and the second sound opening click interval was variable There was no hepatomegaly or peripheral edema. The electrocardiogram revealed normal sinus rhythm probable left atrial enlargement and *non* specific ST segment and T wave abnormalities The chest roentgenogram as compared to the most recent x rays showed left atrial and left ventricular enlargement interstitial edema distended upper lobe veins and interlobar fluid in the minor fissure For the evaluation of function of the mitral valve prosthesis 70 mm fluoroscopic spot films were taken Distortion loss of sperical shape and discontinuity of the superior edge were noticed In systole the disc usually was seated at an abnormal angle with the superior aspect projecting through the ring of the cage toward the left atrial cavity (Fig 1) The diagnosis of variance of the mitral disc prosthesis was made Cardiac catheterization performed on May 5 1972 demonstrated a mitral valve gradient left atrial V wave and left ventricular pressures which varied from beat to beat depending upon the degree of prosthetic malfunction (Fig 2) Mild aortic regurgitation was reconfirmed The left ventricular angiogram showed abnormal motion of prosthetic valve disc and severe mitral regurgitation Immediately following the catheterization reoperation was carried out At surgery the prosthesis was examined and the disc was found to be markedly deficient in substance (Fig 3) It easily lifted out of the cage and was approximately half of its expected size A Starr Edwards ball valve prosthesis (Titanium ball and cloth covered ring Model 6320T) was inserted During surgery the patient developed complete AV block and required ventricular pacing This problem persisted postoperatively and a permanent transvenous Medtronic Demand pacemaker was implanted on May 15 1972 Following an otherwise uneventful postoperative course the patient was discharged on digoxin and warfarin She is asymptomatic at the time of this writing

The pathologic examination of the prosthesis showed no adherent fibrosis or clot around the disc The diameter of the disc measured 2 6 cm as compared to 2 79 cm of the normal

Discussion

The use of intracardiac valvular prostheses during the last decade has prolonged survival and improved the clinical state of patients with advanced valvular heart disease However various late complications such as embolism hemolysis periprosthetic infection detachment of the sewing ring, and thrombosis of the prosthesis are problems faced by these patients after surviving valve replacement Intrinsic ball valve malfunction[1-8] due to degeneration of the ball[23] causing swelling[24] impaction[24,25] fissuring, fracture or fragmentation[23] leading to dislodgement[26] and embolization[23] have been reported with aortic and mitral prostheses of Starr Edwards Smeloff Cutter SCDK Cutter and Magovern Cromie

Low profile discoid prostheses have been used with increasing frequency to replace

been reported more frequently in the mitral position than in the aortic [1,7,24,25] With the development of new valves with silastic occluders ball variance has been only occasionally reported with series 1200 Starr Edwards aortic and other pros thetic valves [9] Abnormalities in the disc mitral valve have been observed in Hufnagel [9,11] Kay Shiley [14,15] Kay Suzuki Cross Jones [17,19] Beall Surgitool [20,21] and Hammer Smith[22] valves In our experience with 60 patients with Harken Surgitool Discoid prostheses this is the only patient who has developed variance Disc variance sec ondary to surface abrasion occurs because of wear of the disc edges producing insuf ficiency of the prosthesis This may vary from beat to beat depending on the disc position across the inflow orifice as was seen in our patient Massive mitral incom petence has also been observed secondary to cocking of the disc [16] Edgett and asso ciates[18] reported intermittent mitral insuf ficiency in four patients produced by an aortic regurgitant jet causing tilting of the prosthetic disc

Whatever the cause of mechanical failure the morbidity and mortality rate associated with prosthetic valve dysfunction necessi tates early surgical intervention even though reoperation is technically more diffi cult and carries a higher surgical risk An operative mortality rate of 13 per cent for patients with ball variance has been re ported by Hylen and colleagues [1] Since the first successful replacement of a thrombosed mitral ball valve prosthesis in 1965 by Spencer and co workers [39] reoperation for replacement of the valve prosthesis has been the treatment of choice in patients with mitral prosthetic dysfunction Herr and associates[4] go a step further in advo cating replacement even in asymptomatic patients having evidence of prosthetic mal function by auscultation and phonocardiog raphy Therefore it seems justified to recommend frequent re examination includ ing phonocardiographic fluoroscopic and where possible echocardiographic evalua tion of all patients with mitral prostheses Whenever there is an acute alteration in clinical status of the patient in the post operative phase complete restudy is im perative The presence of asynchrony ab sence or diminution of prosthetic sounds or appearance of a new murmur persistent or transient should alert a physician to the possibility of ball or disc variance Early recognition of this complication is essential for successful surgical treatment.

Summary

A case of variance of a Harken Surgitool Discoid mitral prosthesis is reported Pros thetic malfunction was suspected because of sudden deterioration of cardiac status after a previously stable postoperative course The appearance of new murmurs as well as variable intensity and timing of the prosthetic sounds were noted in this pa tient The diagnosis was confirmed radio logically and by cardiac catheterization The patient underwent successful replace ment of the mitral prosthesis

The problem of prosthetic variance is discussed with emphasis on diagnostic find ings in malfunction of mitral prosthesis

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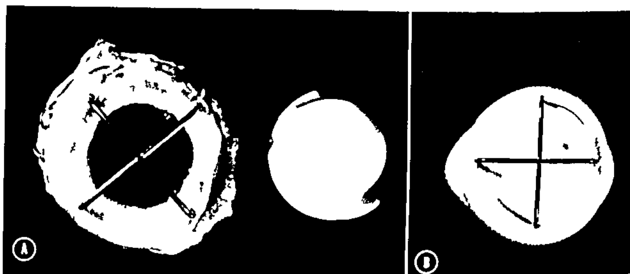


Fig 3 A and B Appearance of prosthetic valves A abnormally worn Harken Discoid mitral prosthesis after removal from this patient B normal prosthesis is shown for comparison

Sudden deterioration in the cardiovascular status in a patient who has been doing well in the postoperative period is a common mode of clinical presentation Acute massive mitral regurgitation resulting from disc valve malfunction has been reported [9,16] The early recognition of ball as well as disc variance by auscultation and phonocardiography has been well described and emphasized [3,4,16,28,32]

Total disappearance or a decrease in the intensity of aortic opening sound as compared to the closing sound is diagnostic of aortic prosthetic ball variance [3,4,28] The presence of variable intensity of the mitral prosthetic opening and closing clicks diminution or complete disappearance of the opening click, and delayed and variable aortic closure–opening click interval, are regarded as characteristic features of mitral prosthetic variance [28,33] The appearance of new cardiac murmurs constant or intermittent, suggests prosthetic malfunction Hylen and colleagues[34] described sound spectrography in the detection of prosthetic dysfunction associated with aortic valve prosthesis and found abnormal sound spectrogram in 78 per cent of patients with ball variance Pfeifer and associates[30] described periodic delayed opening of the mitral valve prosthesis associated with abnormal motion of the cage by echocardiography

Radiological examination of the mitral prosthesis in patients thought to have prosthetic valve dysfunction is a very important diagnostic tool Lansing[35] reported a double exposure appearance of the prosthesis in a prolonged exposure chest film as a common sign of loose mitral valve prosthesis In our patient not only malposition but change in the shape of the disc could be determined on 70 mm cut film x rays

The value of cardiac catheterization to confirm and establish the degree of prosthetic malfunction cannot be overemphasized However it is necessary to be aware of factitious mitral insufficiency or even stenosis[36] caused by inadvertent passage of the cardiac catheter through the struts of the prosthesis when passed retrograde into the left ventricle This may temporarily interfere with motion of the ball or disc

Malfunction of mitral ball as well as disc prostheses due to thrombotic complications causing either impairment of ball movement in the cage [23,30,37] or repeated embolic episodes [24] has been reported Swelling of the ball resulting in critical obstruction to flow through the prosthesis has also been described [24] This has been considered to be due to degeneration of the poppet secondary to the presence of some chemical impurities in its basic material Absorption of blood lipids [38] as well as certain drugs and chemical compounds[24] by a silicon ball leading to its degeneration has been shown by drug diffusion studies and chemical analysis of poppets These problems have been more frequent with series 1000 Starr Edwards aortic prosthesis than in the Starr Edwards mitral valve [1,3,6,27] In contrast with Smeloff Cutter prosthesis ball variance has

Nonpenetrating cardiac injuries A collective review

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Violent injury now accounts for the majority of deaths among persons below the age of 40 years and as described recently by the National Research Council of the National Academy of Sciences represents the neglected epidemic of modern society[1] In a consideration of the sequelae of injury to various organ systems cardiac damage is particularly hazardous and accounts for one of the leading causes of death in traumatic injury However its diagnosis is often difficult and as recently stated by the medical examiner for the City of Philadelphia represents the commonest unsuspected visceral injury responsible for death in fatally injured accident victims in that city[2] If this estimate is correct then presumably the incidence of heart damage may be much higher in rural areas where deceleration injuries account for much larger proportions of death[3]

Whereas penetrating wounds to the chest involving the heart are seldom unsuspected by virtue of the nature of the wounds nonpenetrating chest trauma injuring the heart is often found in combinations with other organ system injuries including major fractures ruptured viscera and other less serious but more noticeable injuries all of which tend to overshadow and obscure the cardiac damage A recent review by Parmley and colleagues[4] demonstrates the infrequency with which the diagnosis is made In 353 instances of myocardial rupture secondary to nonpenetrating trauma discovered at autopsy a cardiac lesion was suspected only once prior to death Quite obviously injuries associated with less hemodynamic derangement are even more likely to be overlooked by clinicians

Although young adults are most frequently the victims of nonpenetrating heart injury all age groups are susceptible Cardiac injury has been described in the in utero fetus due to maternal injury[5] during labor and delivery[6,7] and in very early childhood[8]

Although nonpenetrating heart injuries have been described in sporadic case reports for hundreds of years Beck[9] was the first to systematically document this entity by his clinical and laboratory observations in 1935 It is the purpose of the present communication to extend these observations first by reviewing the several types of cardiac lesions found in nonpenetrating trauma second by presenting more recent data relating pertinent clinical manifestations and diagnostic clues and lastly by discussing currently available information concerning therapy

Mechanisms of injury

Before the days of high speed automobile travel nonpenetrating chest trauma with subsequent heart damage was quite un

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Hemopericardium tamponade and effusion Cardiac tamponade may occur in association with any cardiac injury which produces hemopericardium and repeated pericardiocentesis may be required[27, 28] *Tamponade may appear* as long as a week or more following injury and prompt pericardiocentesis may be required to avert catastrophe Although pericardiocentesis is widely acclaimed in the treatment of localized *penetrating wounds* to the heart its role in the treatment of most myocardial wounds due to blunt trauma is limited by the usually greater extent of myocardial damage present and by the nonlocalized nature of the damage *On occasion retained* blood can lead to late occurring chronic pericarditis with constriction months or years afterwards which may necessitate pericardiectomy

Pericarditis Some degree of traumatic pericarditis usually from pericardial and/or myocardial ecchymosis or hematoma is found at postmortem in most cardiac injuries due to blunt chest trauma Although occasionally reported to be of clinical significance resolution from this disorder is the rule Should however intracardiac surgery be required later obliteration of the pericardial sac may cause technical difficulties at operation especially if the cardiac defect has resulted in cardiac enlargement[30]

Delayed recurring pericardial effusions acute pericarditis and chronic constrictive *pericarditis may follow both* closed and penetrating cardiac injuries[31, 32] Among five cases reported by Guest and colleagues[32] three followed blunt injury Why some patients go on to develop recurrent pericarditis *or constriction is not well understood* but Tabatznik and Isaacs[33] believed recurrent inflammation to be present secondary to an altered autoimmune process which sometimes responded to corticosteroid administration The *vast majority of patients* with late-occurring constrictive pericarditis however show no demonstrable cause Extensive calcification of the pericardium[34] has been described as an additional long term complication in this *setting* and Mannix and Dennis[35] have recommended pericardiectomy in cases which become symptomatic

Myocardial contusion In the context of modern cardiac surgery myocardial contusions may seem trivial and *of little clinical* consequence yet well documented instances of death following this lesion have been recorded for hundreds of years[36, 38] The first case of unquestionable myocardial contusion reported by Akenside[10] in 1764 was in a 14 year-old boy who died 6 months after injury However it was not until 1935 that Bright and Beck[19] working with a trauma preparation in dogs first called attention to the significant pathophysiologic consequences that form the basis of our modern concepts concerning this lesion

To understand the signs and symptoms *of myocardial* contusion it is helpful to review the pathological changes in the myocardium The external appearance of the heart may show little if any evidence of injury yet a small area of subepicardial *hemorrhage may overlay a much* larger area of intramural contusion Extensive contusion of the intraventricular septum can exist in the absence of other gross evidence of injury The transition from normal to damaged myocardial tissue *is* usually abrupt in contusion in contradistinction to myocardial infarction where more gradual transitions occur Otherwise the histological changes are similar in the two lesions with myocardial cell necrosis infiltration of polymorphonuclear leukocytes absorption of hemorrhage and healing by scar formation occurring in both Ultimate healing of both contusions and infarcts may be virtually identical and differentiation between the two processes at a later time must rely on history condition of the coronary *arteries* and other evidence[39, 41] When extensive damage is present throughout the myocardium early death is the rule although some later deaths have been recorded Causes of death include ventricular *fibrillation*[19] *pro*longed cardiac standstill[21, 42, 43] myocardial rupture and/or heart failure[44, 45]

Clinical manifestations and diagnostic criteria for myocardial contusion follow closely from the similarity with *myocardial* infarction In a group of verified cases gathered from the literature fully 70 per cent of patients with myocardial contusion reported chest pain identical with that customarily associated with *the onset of coronary* occlusion[38] Most patients had concomitant chest wall injuries with resultant musculo

Table I Classifications of cardiac lesions in nonpenetrating chest trauma

I Pericardium
  A Disruption
  B Hemopericardium and tamponade
  C Pericarditis
II Myocardium
  A Contusion
  B Rupture
  C Septal perforation
  D Late aneurysm
III Valves chordae tendinae and papillary muscles
IV Coronary arteries
  A Contusion and thrombosis
  B Laceration

usual, yet occasionally such accidents were recognized[10-13] and lethal arrhythmias and myocardial rupture were described[4,13-15] With the advent of the automobile however high speed deceleration impact injuries have markedly increased and currently represent by far the commonest cause of this type of lesion Vehicular impact abrupt transfers of kinetic forces to the victim and sudden decelerations of bodily viscera and blood column momentum all operate sequentially to produce cardiac damage The extent and severity of this injury is determined by several biomechanical interactions including the magnitude of deceleration the total duration of exposure to the forces of deceleration, and the rate of time change of deceleration, according to Newtonian laws of dynamics

$$F = MA$$

or in the case of deceleration $F = MD$

and $D = V_2 - V_1/t$

where F is the resultant of forces acting on the viscera M is the scalar mass of the viscera involved D is the magnitude of deceleration V_2 and V_1 are terminal and initial velocities respectively and t is the time duration of velocity change

Stapp[17] and Lasky and colleagues[18] have also described an additional hydraulic ram effect as contributing to the development of heart damage in selected injuries in which abdominal and lower extremity compression may upwardly displace abdominal contents and produce cardiac injury in the absence of actual thoracic trauma Bright and colleagues[19] Arenberg[20] and others[21-23] observed internal thoracic damage to be less in cases of nonpenetrating chest trauma in which skeletal rib fractures have occurred suggesting a protective influence of the thoracic wall in dissipating energy impact forces This is supported by the data of Dunseth and Ferguson[3] who noted in cases of severe myocardial damage—i e , 17 cases of ventricular septal rupture—that only 5 had sternal or rib fractures

Classification of cardiac injuries

The lesions to be discussed are categorized by type and location in Table I While some structures appear more resistant to damage than others injuries to all structures have been reported both singly and in combination When multiple the physiological consequences of each injury may interact to either preserve function or cause deterioration and/or death especially where pericardial involvement exists

Pericardial disruption How often pericardial rupture occurs in survivors is unknown *Parmley and colleagues*[4] found pericardial disruption in 71 of 546 autopsy cases A higher incidence of pericardial tears was reported by the present authors[4] in an experimental animal model preparation in 14 of 18 dogs receiving sublethal blunt chest trauma Almost all rents were transverse and extended across the upper base of the heart near the reflection of the visceral and parietal pericardium The clinical implications and sequelae of this rupture as an isolated lesion are the potential danger of cardiac herniation[25] with catastrophic hemodynamic compromise and possible death

Boyd and Strieder[26] pointed out that when myocardial and pericardial defects coexist particularly with bleeding survival was largely dependent upon the relative size of the pericardial tear or conversely upon the degree to which the integrity of the pericardial sac was preserved to prevent exsanguination With large tears death was inevitable With sufficiently small disruptions however adequate tamponade may control myocardial bleeding long enough to permit surgical intervention If both pericardial and myocardial wounds are small stabilization without treatment may proceed to complete recovery

presence of cyanosis heart failure dyspnea or orthopnea Interestingly coronary vasodilators and anticoagulants have proved of little benefit for this lesion

Myocardial rupture Myocardial rupture is the lesion most frequently found at autopsy following fatalities due to non penetrating chest trauma In addition to violent impact injuries closed chest massage in cardiopulmonary resuscitation has added to the frequency of this lesion In order of frequency rupture of the right ventricle occurs most often followed by the left ventricle right atrium and left atrium [4] Its occurrence in relation to nonpenetrating chest trauma carries a much graver prognosis than with penetrating wounds primarily due to the greater extent of damage Penetrating defects of the myocardium have been frequently repaired successfully by surgical correction whereas closed chest lesions have rarely been corrected One series reported only 30 of 152 patients with ventricular chamber rupture to survive 30 minutes or longer following trauma [19] Recently however encouraging reports have appeared documenting survival in a small series of surgically repaired atrial ruptures [79 82] In these patients hemopericardium tamponade and cardiac failure were tolerated for longer periods of time thus allowing for more optimal surgical interventions including cardiopulmonary assist devices

Physical findings of myocardial rupture in those patients surviving long enough to reach the hospital are characteristic of cardiac tamponade Depressed arterial blood pressure distended neck veins with an elevated central venous pressure muffled heart sounds pericardial friction rub and an enlarged cardiac shadow on chest film are all expected findings The electrocardiogram shows diffuse low voltages

Treatment consists of emergency surgery Too few survivors have been encountered to establish the benefit of interim pericardiocentesis but this seems doubtful as a therapeutic tool since blood loss is too massive Time and facilities permitting extracorporeal assist devices seem of great potential merit but in view of the fact that 75 per cent of high speed accident injuries occur in or near communities with populations of 2 500 people or less [8] undue insistance upon having these sophisticated devices present before attempting repair may result in further loss of life

Surgical techniques found to be of use in penetrating wounds of the heart should also prove effective with nonpenetrating cardiac injuries The widest possible exposure is mandatory Digital occlusion of ventricular perforations and occlusive clamps applied to atrial defects will control bleeding while sutures are applied In inaccessible areas the insertion of a balloon catheter through the tear with inflation and traction may be helpful in controlling bleeding during repair

Septal perforation Despite its seemingly protected anatomical position the interventricular septum appears acutely susceptible to injury secondary to nonpenetrating chest trauma [84 87] Predilection for septal perforation particularly near the apex is high [88] Many reports of this lesion are described in the literature [10 83 87 89 93] Inkley and Barry [94] noted in animal studies an increased risk of vulnerability when the traumatic blow was interjected late in diastole or early systole [94]

Diagnosis may be difficult since rupture of the chordae tendinae and/or papillary muscles with mitral or tricuspid incompetence severe myocardial contusion with congestive heart failure or pre existing congenital defects all may mimic acquired septal perforation An easily palpable precordial thrill and early holosystolic murmur maximal in the third and fourth intercostal spaces at the left sternal border are the characteristic findings but may be absent in the presence of shock The electrocardiogram may show left axis deviation left anterior hemiblock and/or right bundle branch block indicating multifascicular injury to conduction pathways Currents of injury [95] and several rhythm disorders [2 70 88] have also been described Cardiac catheterization affords the only reliable means of establishing the correct diagnosis [96]

Although small defects may close spontaneously the treatment of choice is surgical closure particularly in the presence of cardiac failure [97 99] There have now been reported more than 20 surgical repairs for traumatic perforations of the interventricular septum [45 86 90 93 100 101] Peirce and col

skeletal pain, but many of those with myocardial bruises had, in addition readily distinguished angina like symptoms which interestingly were not relieved by coronary vasodilating drugs

Diagnosis of myocardial contusion is rarely obvious on physical examination alone in the absence of major complications such as pericardial tamponade [28 46 48] cardiac arrhythmias [49 52] or heart failure [44 45] Tachycardia is invariably present in this setting but may be in response to associated injuries as well as heart damage

Twelve lead electrocardiography has proved to be the most reliable means of making the diagnosis of myocardial contusion in patients with thoracic injury Despite possible errors in specificity [53 54] electrocardiography offers an accurate practical and dependable means of evaluating the injured patient The time course of changes in the electrocardiogram following cardiac trauma is not completely known but from the data available in the absence of arrhythmias fully a third of patients in the first 24 to 48 hours after injury will develop ST segment and T wave changes similar to myocardial ischemia and/or infarction [37 55 59] The duration of these changes varies but may persist for as long as a month following injury These observations have been duplicated in several animal studies [43 47 60 61] in which similar electrocardiographic changes were reported including transient elevations of the ST segment and T waves suggesting a current of injury pattern

Electrocardiographic changes which persist for periods of longer than a month and become permanent suggest lesions more complicated than simple contusion and include extensive myocardial scarring with possible left ventricular aneurysms and coronary artery injury which will be discussed in later sections

A wide range of rhythm disorders and conduction disturbances have also been documented, both in clinical and in animal studies Cardiac arrhythmias have included premature ventricular contractions (the commonest type of dysrhythmia) complete cardiac standstill, second third and varying degrees of heart block, atrioventricular dissociation with or without interference, ventricular tachycardia and fibrillation and atrial tachycardia flutter, and fibrillation [19 24 43 49 51 62 67] Conduction disturbances have included right and left bundle branch blocks and interventricular conduction delays [52 68 71] Aside from a weak correlation between these disorders and severity of injury, their mechanism of development is not understood despite extensive autopsy analyses of clinical and animal material [11 41] Direct response to injury interplay of *neurohumeral reflexes coronary* spasm and effects of intramyocardial hemorrhage have all been suggested [19 43 65 72 74]

Other laboratory studies have not proved of much help in the diagnosis of myocardial contusion Serum enzyme changes are so frequently elevated in concomitant injuries of the liver lung bone brain and skeletal muscle that specificity for cardiac injury is essentially masked [37 59 75] Shubin and Weil[76] and Vessel and associates[77] showed significant elevations of serum glutamic oxaloacetic transaminase (SGOT) and lactic dehydrogenase (LDH) in hemorrhagic shock per se which would limit their usefulness should major blood loss develop in association with cardiac injury Studies in combat casualties[78] showed elevations in SGOT and LDH not only in shock but also in metabolic acidosis and lactic acidemia, which would further lessen their usefulness in the diagnosis of myocardial contusion

Other laboratory tests such as leukocyte count and sedimentation rate also lack sufficient specificity for myocardial contusion but may be helpful in following the clinical course of the patient to determine optimal times at which physical activity may be resumed From a medicolegal standpoint all laboratory aids which can be employed with little risk to the patient should be used if the clinician believes they may help in assessing residual damage to the myocardium

In general the treatmeat of myocardial contusion is similar to that of myocardial infarction Bed rest is most important usually for a 2 to 4 week period followed by a program of graded ambulation Specific drug therapy should be strictly supportive Digitalis is only effective in the control of heart failure or supraventricular tachyarrhythmias Oxygen is indicated in the

results [121] and prosthetic valve replacement is now recommended as the procedure of choice [122]

Injuries of the mitral valve may involve tears of the anterior and/or posterior valvular leaflets but more commonly cause ruptures of the chordae tendinae and papillary muscles [112 1 3 128] The mitral valve appears most vulnerable to rupture during diastole when the heart is distended Rupture of a mitral valve chordae tendinae or papillary muscle is accompanied by the development of precordial pain breathlessness palpitation shock or fulminating left heart failure A precordial thrill with a loud harsh holosystolic murmur maximal at the apex and radiating to the axilla is present on physical examination An apical diastolic murmur indicating torrential return of blood across the mitral valve may also be heard and cardiac enlargement usually develops with time Rupture of a papillary muscle is catastrophic and leads to rapid development of left heart failure with death in hours or days Early operation affords the best chance of survival Methods of repair have historically been individualized with successes reported both with valvuloplasty and prosthetic valve replacement [125 126] The latter is fa ored currently by most clinicans

Traumatic injury of the tricuspid valve with dysfunction and insufficiency is fortunately rare In 1848 Todd[129] first reported this injury and accurately described the pathophysiology leading to its damage He concluded that violent external cardiac compression plus sudden pulmonary outflow obstruction put great strain on the chordae tendinae and papillary muscle attachments to the tricuspid valve leading to tears and rupture Jahnke and associates[130] as recently as 1967 reviewed the world literature on traumatically acquired tricuspid insufficiency and found 12 cases Since then Morgan and Forker[131] have reported on three others and Madoff and Desforges[132] have reported on one The majority of patients were men most trauma involved automobile accidents and the described lesions included ruptured papillary muscles chordae disruptions or detachments valve leaflet rupture and complete valve destruction

Symptoms of tricuspid incompetence vary from mild to severe and include fatigue massive peripheral congestion with ascites and edema and occasionally dyspnea and orthopnea Similar to mitral valve dysfunction disruption and tearing of the papillary muscles following injury has produced the most fulminant tricuspid insufficiency with rapid clinical decline Physical findings include central venous hypertension with obvious V wave pulsations in the neck hepatic pulsations with positive hepatojugular reflex and a loud holosystolic murmur heard along the lower left sternal border which increases with inspiration

In the group reviewed by Jahnke and colleagues [130] 10 had electrocardiograms and 8 showed complete or incomplete right bundle branch block On fluoroscopic examination marked paradoxical pulsation of the right atrium and superior and inferior vena cavae were seen Cardiac catheterization done in 9 demonstrated ventricularized atrial pressures in systole with giant V waves ranging from 8 to 28 mm Hg Six patients were operated on between three months and ten years after injury and three received prosthetic valves Primary repair of the papillary muscles has also been attempted in a few [4 133 134] but results have proved poor and valve replacement in sufficiently compromised patients now appears to be the procedure of choice [4 130 132 134 139]

Coronary arteries The question of whether nonpenetrating chest trauma can cause direct injury to the coronary arteries either by thrombosis laceration or occlusion has been strongly *debated in* the literature[4 140 144] for some time Evidence from several sources would support such a relationship [145 150] *but further* and more direct documentation particularly with coronary arteriography is required Nevertheless *when electrocardiographic* evidence of myo*cardial infarction* is obtained shortly after *injury in* a young individual with no prior *history* of heart disease and these changes *persist* permanently the differential diagnosis should include traumatically acquired coronary artery hemorrhage and/or occlusion

At the present time too few numbers of unequivocal cases *representing* this syndrome are currently *available* to recommend definitive courses of therapy How

leagues,[45] who reviewed the histories of 18 patients not operated on found that 10 died of congestive heart failure within 15 days of their injuries This experience serves to emphasize the urgency of pro ceding promptly with cardiac catheteriza tion and surgical repair

Late aneurysm This complication of non penetrating injuries to the heart, if accom panied by advanced symptoms of failure, has rarely been treated successfully to date Its true incidence is unknown since many of those which cause little disability probably go undiagnosed In those instances where myocardial aneurysm is recognized it is not certain whether myocardial contusion directly[102] or in combination with coronary artery disease acquired either secondarily as a response to trauma or developed sepa rately on an atherogenic basis has caused formation of the aneurysm

In addition to true aneurysm myocardial contusion and small ruptures may also produce pseudoaneurysm O Reilly[103] re viewed 15 cases of ventricular aneurysm following nonpenetrating chest trauma nine of which were in children and found that where the character of the lesions was clearly described three were true and five were false or pseudoaneurysmal

Morbidity and mortality statistics in both types of aneurysm are high with fatal complications including myocardial rup ture and tamponade cardiac failure sys temic emboli and arrhythmias causing sud den death [104] Lyons and Perkins[105] reported the first operative treatment for post traumatic left ventricular aneurysm in 1958, and preliminary results from studies reported by Killen and associates [106] Aron stam and colleagues,[104] and Pupello and co workers [107] as well as from the increasing experience with management of post infarc tion aneurysm [108] suggest this mode of therapy may soon become the accepted treatment of choice

Valves chordae tendinae and papillary muscles Prior to the advent of open heart surgery, injuries to cardiac valves and their supporting structures were irreparable, and except in instances where the hemo dynamic sequelae were mild, therapy was ineffective Some form of corrective treat ment is now available for almost all such injuries and early diagnosis may avoid serious disability or death Untreated rupture of a valve is usually followed by rapid progression of congestive heart failure with eventual demise within a year or two

Historically, these lesions have generated considerable curiosity and interest in the literature beginning with Barie,[109] who in 1881 demonstrated in cadavers that ex treme pressures were required to rupture cardiac valves Dufoeur [110] as early as 1891, experimentally produced aortic rupture in dogs A variety of traumatic mechanisms postulated to cause these lesions were inves tigated including direct chest wall impact, abdominal and lower extremity compres sion, various strains and blast pressure from explosions [111 112] Kulbs[113] concluded that only modest increases in intra aortic pressures were required to cause aortic valve rupture and ascribed the greater fre quency of left sided valve injuries to higher pressures in these chambers Pre existing condition of the valves is also important as Freidberg[114] reported a greater incidence of traumatic valve ruptures in those pa tients with pre existing disease in either the mitral and/or aortic valves

In order of frequency traumatic impact injuries produce rupture of the aortic valve most often followed next by damage to the mitral valve [115 119] Howard[111] has reviewed the literature on aortic insufficiency and has found 44 believed to be due to trauma or strain Of these 22 valves showed rup ture along the base at the annular attach ment of the cusps 11 had tears in one or more of the cusps in 2 of which all 3 cusps were torn and 10 of the valves were frankly detached from the aorta This complication occurred overwhelmingly in men

In aortic lesions there is a typical high pitched diastolic blowing murmur heard with the usual circulatory hemodynamic changes associated with aortic regurgita tion [120] A distinctive musical murmur de scribed as ' sea gull or cooing dove in character has also been attributed to aortic valve rupture but is not invariably present Cardiac catheterization and supravalvular angiography are essential in identifying this lesion and early recognition is mandatory in order to avert the complications of massive cardiac insufficiency with left ventricular failure Primary repair of the damaged valve was attempted early with poor

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ever treatment should be supportive and similar to the management of other forms of acute myocardial infarction Whether future management for this complication will include the newer surgical revascularization procedures such as aortocoronary saphenous vein bypass graftings remains speculative at this time

Summary

Nonpenetrating chest trauma with injury to the heart has become increasingly common particularly as a result of deceleration injuries in modern, high speed vehicular accidents The present report reviews the currently available information concerning the several varieties of cardiac lesions which are incurred including damage to the *pericardium*, myocardium, valvular structures and coronary arteries Although highly lethal if neglected and often obscured by associated trauma cardiac damage can generally be estimated quickly with a proper index of suspicion and relatively simple diagnostic tools Modern medical and surgical techniques in the appropriate clinical settings have proved curative

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Fig 1 A and B A Mitral and B aortic echograms from a normal subject The individual echoes from the valve leaflets are sharp and free of any thickening or shaggy echoes Valvular motion is unrestricted *AMV* = anterior mitral valve leaflet *PMV* = posterior mitral valve leaflet *AAV* = anterior aortic valve leaflet *PAV* = posterior aortic valve leaflet

surgery or their hearts were examined at autopsy All patients had numerous blood cultures

Results

Four of the eight patients were found to have positive blood cultures *Streptococcus viridans* was the organism in three of the patients The blood culture in the fourth patient grew enterococcus The four patients with negative blood cultures had received prior antibiotic treatment before transfer to this facility but had clinical evidence of bacterial endocarditis and were appropriately treated At autopsy or surgery five patients had vegetations on the aortic valve and three had vegetations on the mitral valve Of the three patients with mitral valve lesions the vegetations were on the anterior leaflet in one the posterior leaflet in another and on both leaflets on the third The vegetations in all of the patients varied from 2 to 8 mm in size

Fig 1 shows mitral valve and aortic valve echograms from a normal subject Figure 1*A* shows the anterior and posterior mitral valve leaflets while the anterior and posterior aortic valve leaflets are demonstrated in Fig 1*B* It should be noted that these echoes are sharp and free of any thickening or shaggy echoes attached to the valve Fig 2 is a composite of several views of the aortic valve echogram from a patient in whom the aortic valve was involved with vegetations The echograms are characterized by a non uniform thickening in several areas of the valve In many areas the thickened valve has a shaggy appearance Although these shaggy echoes are seen in each view of the aortic valve the individual echograms are slightly different demonstrating the non uniformity of this abnormality These different echograms also illustrate why it is usually necessary to scan the entire valve to be certain to visualize any abnormality In Fig 2*C* the aortic valve appears to be free of any abnormal echoes during systole and the abnormal shaggy material occurs during diastole In Fig 2*B* the abnormal echoes seem to be seen best during systole A consistent observation in all of the views is that despite the apparent thickening of the aortic valve leaflets the valve motion remains normal [2,3] The other four patients with pathologically proved vegetations on the aortic valve had echocardiograms similar to those exhibited in Fig 2

Fig 3 is a mitral valve echogram from a patient who has valvular vegetations of the anterior leaflet of the mitral valve There is uneven thickening noted under the anterior leaflet This thickening can be noted both during systole and diastole Despite this

Fundamentals of clinical cardiology

Echocardiographic manifestations of valvular vegetations

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The presence of vegetations on cardiac valves is a hallmark of bacterial endocarditis[1] This study was undertaken to see if echocardiography could visualize such vegetations and if so to determine what size these vegetations would have to be in order to be seen by echocardiography Hopefully if these vegetations could be visualized by echocardiography this information might not only be useful diagnostically, but it might provide some information concerning the pathogenesis and natural history of this disease

Method

Eight patients with either surgically or autopsy proved valvular vegetations were evaluated using echocardiography The echocardiograms were obtained using an Ekoline Mark IIA echocardiograph coupled to an Electronics for Medicine recorder A 2 25 MHz, 0 5 inch transducer, focused at 7 5 cm was employed in all patients The patients were examined in the recumbent position The transducer was placed in the third or fourth intercostal space along the left sternal border The transducer was directed posteriorly and slightly medially in order to pick up the mitral valve echoes The transducer then was rotated superiorly and medially towards the right shoulder to pick up the aortic root and valve If the aortic valve cusps were not obtained in this position the transducer was usually moved up one interspace and again pointed superiorly and medially Both the mitral and aortic valve echoes were obtained in all eight patients In doing the echocardiographic examination emphasis was placed on an M mode scanning technique whereby the direction of the transducer is changed while recording continuously[2] This technique permits the recording of many views of each valve in a continuous recording It avoids the problem of having the echogram vary with the direction of the transducer and also provides a more complete examination of the particular valve in question

All patients either underwent open heart

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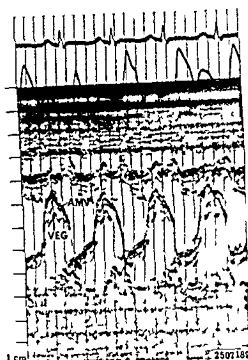


Fig 3 Mitral valve echograms from a patient with vegetations on the anterior mitral leaflet There are multiple echoes (*VEG*) on the anterior leaflet (*AMV*) originating from the vegetations Despite this apparent thickening of the leaflet the valve motion remains unrestricted and there is actually some coarse fluttering of the valve during diastole

a shaggy appearance and is non uniform with respect to the areas of the valve which are involved

Whether or not these echocardiographic findings are specific for valvular vegetations remains to be proved There does not seem to be any problem in confusing these echograms with the usual causes of thickened mitral or aortic valves [2,9] Fig 6 shows the mitral valve echograms from two patients with mitral stenosis In one patient there is minor thickening of the leaflets with abnormal motion and a decreased diastolic slope In Fig 6*B* the mitral valve is heavily calcified with a large band of echoes noted throughout the valve The dense echoes are not spotty and the valve motion is definitely abnormal [4,7]

Fig 7 contains echocardiograms from a patient who has another condition that could be confused with valvular vegetations This patient has a left atrial myxoma There are several differentiating features

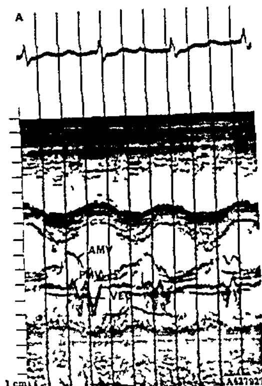


Fig 4 Echocardiogram from a patient with vegetations involving the posterior mitral leaflet The vegetations are recorded as a block of shaggy echoes (*VEG*) attached to a freely movable posterior mitral valve leaflet (*PMV*) The anterior mitral valve leaflet (*AMV*) is thin and apparently uninvolved with vegetations



Fig 5 Surgical specimen of the mitral valve from the patient whose echogram is seen in Fig 4 The large vegetation involving the posterior leaflet is easily seen (*arrow*) Note also the perforated anterior leaflet and the ruptured chordae

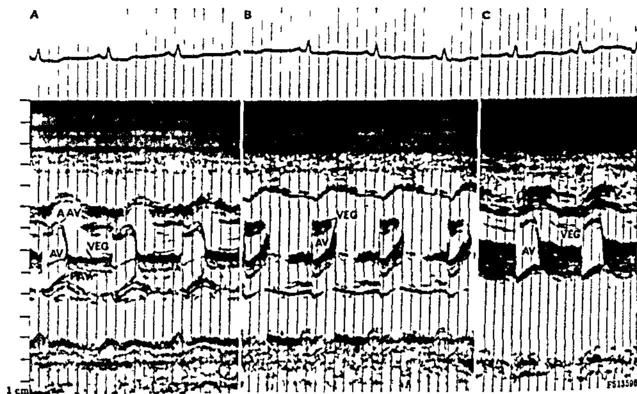


Fig 2 *A* through *C* Three aortic valve echograms from a patient with vegetations on the aortic valve The location and appearance of the vegetations vary depending upon the angle of the transducer and how the ultrasonic beam strikes the valve Despite the apparent valvular thickening the motion of the leaflets remains unrestricted *AAV* = anterior aortic valve leaflet *AV* = aortic valve *PAV* = posterior aortic valve leaflet *VEG* = vegetation

apparent increase in the amount of valvular echoes, the motion of the valve remains unrestricted and even exhibits some coarse fluttering during diastole[4,7] Fig 4 is another echocardiogram from a patient with bacterial endocarditis and vegetations on the mitral valve In this patient, the vegetations were confined solely to the posterior leaflet The large shaggy echo attached to the echo of the posterior leaflet is easily seen (*VEG*) Again the motion of the posterior mitral leaflet is good[8,9] despite the presence of this large echo producing mass Fig 5 is a photograph of the mitral valve following surgical removal from the patient whose echogram is seen in Fig 4 The large vegetation on the posterior leaflet is noted by the arrow The echogram from the patient who had vegetations on both mitral leaflets demonstrated shaggy echoes on both leaflets with the motion of the leaflets remaining unrestricted In all eight patients, the location of the echocardiographic valvular abnormalities correlated with the location of the vegetations at surgery or autopsy

We were able to obtain serial echograms on two of the eight patients with vegetations In these two patients, the intensity and size of the echoes presumably originating from the valvular vegetations, increased with time despite the patients apparent bacteriologic cure both clinically and by culture of the surgical specimen

In one patient who proved to have bacterial endocarditis confined to the aortic valve the echocardiogram was considered to be positive for vegetations before the diagnosis was expected clinically This patient had chronic renal failure and was undergoing echocardiography to rule out pericardial effusion

Discussion

The results of this study seem to indicate that echocardiography can detect valvular vegetations provided that they are at least 2 mm in diameter The echocardiographic manifestations of these vegetations seem to be an apparent thickening of the valve with no restriction in motion of the leaflets In addition, the thickening frequently has

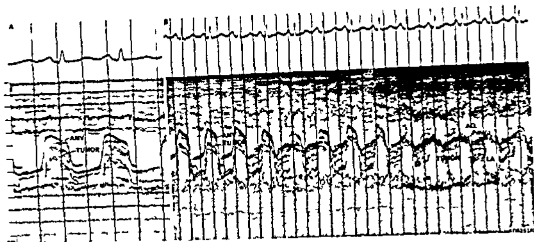


Fig 7 *A* and *B* Echocardiograms from a patient with a left atrial tumor The tumor echoes in echogram *A* superficially resemble echoes arising from vegetations *One differentiating feature* is that the tumor obscures the echo from the posterior mitral leaflet In echogram *B* directing the ultrasonic beam toward the left atrium (*LA*) one continues to record tumor echoes in the left atrium indicating that the echoes most likely originate from a mass in the left atrium rather than from vegetations attached to the valve leaflet

echocardiography to be done serially provides an excellent opportunity to study the natural history of patients with treated bacterial endocarditis It is quite possible that many patients with apparently cured bacterial endocarditis go on to form thickened and significantly deformed valves

Unfortunately it could not be determined from this study as to when in the course of illness the vegetations appeared because the exact onset of the illness was not known in many of the patients We have examined some patients with clinically evident bacterial endocarditis in whom we were unable to demonstrate any valvular vegetations None of these patients went to surgery or autopsy This observation raises the question as to how much time is required from the onset of the illness until vegetations can be seen echocardiographically In addition it is possible that in the successfully treated case of endocarditis the vegetations may never get large enough to be recorded on the echogram These questions obviously must be answered before the echocardiographic technique can be fully evaluated as to its usefulness in the diagnosis of bacterial endocarditis Thus although this study demonstrates that echocardiography can detect valvular vegetations secondary to bacterial endocarditis and that such examinations may prove to be useful in enhancing our understanding as to the role of vegetations in this disease the specificity of this echocardiographic finding must yet be proved and the exact role of this technique in the diagnosis of bacterial endocarditis must be studied further

Summary

Eight patients with autopsy or surgically proved valvular vegetations were examined using echocardiography Five of these patients had lesions on the aortic valve and three had lesions on the mitral valve The echocardiographic finding in these patients was a non uniform thickening of valve leaflets which exhibited unrestricted motion Often the abnormal echoes which produced the thickened valve had a shaggy appearance In all eight patients the location of the echocardiographic abnormality correlated with the anatomic findings at surgery or autopsy In one patient the diagnosis of bacterial endocarditis was first suspected following the echocardiographic examination and only subsequently was a heart murmur heard These findings indicate that echocardiography may play a useful role in elucidating the pathological anatomy of the bacterial endocarditis with vegetation however the length of time from the onset of clinical

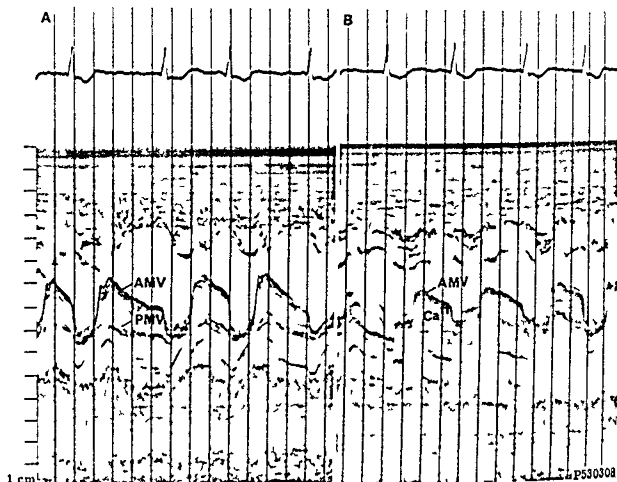


Fig 6 *A* and *B* Mitral valve echograms from two patients with mitral stenosis The valve in echogram *A* is mildly fibrotic whereas the mitral valve in *B* is heavily calcified Both valves exhibit uniform thickening of the leaflets and the calcium (*Ca*$^{++}$) in *B* has a shaggy appearance Both valves can be distinguished from patients whose thickened valves are due to vegetations by the abnormal motion characteristic of mitral stenosis

which distinguish this echogram from those taken of patients with valvular vegetations [10-12] In Fig 7*A* the posterior mitral valve leaflet is not seen because it is obscured by the tumor In addition the extra echoes do not seem to be directly attached to the valve leaflets Possibly the most convincing evidence that the patient in Fig 7 had a left atrial tumor and not valvular vegetations is the fact that the tumor continues to be seen as the ultrasonic beam is directed towards the left atrium Valvular vegetations are attached to the valve and have not been noted in the left atrium

We have had one patient with myxomatous degeneration of the mitral valve who exhibited thickening of the posterior mitral valve on the echocardiogram The leaflet motion continued to be good and the valve did not look like one which was scarred by rheumatic disease The appearance of the valve was different from those with vegetations in that the thickening was fairly uniform and the echoes did not appear shaggy However it should be noted that not all of the patients with vegetations had the shaggy echoes on the valve (Fig 3) Thus there could conceivably be some confusion between the echograms of patients with vegetation and those with myxomatous degeneration and thickened valves

The fact that two patients had a progressive increase in the intensity and size of the echoes originating from the vegetations despite an apparent bacteriologic cure raises several interesting questions The development of increased echoes could represent a normal healing process and not necessarily a progression of active infection Obviously, further studies are necessary to answer this question but the ability of

Complications of aortocoronary artery bypass surgery

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The effectiveness of aortocoronary artery bypass grafting in the treatment of occlusive coronary disease is related to selectivity of patients surgical technics and skills and the subsequent course of the disease process Expertise and experience with heart lung bypass operations in general have minimized operative risks but there are specific complications of coronary artery grafting which must be considered in the evaluation of these procedures

Myocardial infarction in the intraoperative and early and late postoperative periods fate of the arteries proximal and distal to the site of anastomosis continued patency of the grafts and the progression of disease in grafted and ungrafted vessels are important factors in the late morbidity and death of the patient

Myocardial infarction

Variability in interpretation of early postoperative electrocardiograms has made the frequency of acute myocardial infarcts during surgery difficult to determine Persistence of the serum isoenzymes of lactic dehydrogenase and the cardiac specific myoglobin fractions of creatine phosphokinase may supplement the diagnosis of equivocal electrocardiographic changes

The operative mortality rate of most reported series varied from less than 3 per cent to about 10 per cent Evidence of acute myocardial infarction as manifest by the appearance of abnormal Q waves was present in more than 50 per cent of the deaths in whom early postoperative electrocardiograms were available Anatomic evidence of myocardial infarction was found in almost 60 per cent at autopsy In some instances of necropsy proved necrosis the electrocardiograms were not definitely diagnostic

Approximately 15 per cent of patients surviving coronary bypass grafting may have definite electrocardiographic evidence of acute myocardial infarction If occurrence of left bundle branch block and left anterior hemiblock are included 17 to 18 per cent of survivors have myocardial necrosis during surgery

The total frequency of acute myocardial infarction during coronary bypass grafting appears to be in the range of 20 per cent of all patients both survivors and those succumbing to surgery Since repolarization abnormalities of the electrocardiogram are almost universal in the early postoperative period subendocardial and small intramural infarctions may be missed by the strict criteria of Q wave appearance and

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illness to echocardiographic diagnosis remains unknown

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internal mammary artery more closely approximates the caliber of the distal coronary artery than the larger saphenous vein has furthered the recent interest in this technic In addition to the internal mammary direct anastomosis to the left anterior descending and circumflex arteries free grafts of this artery have been used for aorto right coronary artery bypass Indeed in some instances the splenic artery has been brought through the diaphragm to the right coronary artery Too few arterial grafts of these various types have been done to assess adequately their effectiveness and complications

Progression of coronary artery disease after bypass grafts

Progression of stenosis in the coronary artery proximal to graft anastomosis apparently is quite common This portion of the vessel may become totally occluded in a large number of cases It has been demonstrated in as many as 60 per cent of instances in which vein grafts were non patent within two weeks of operation and in 20 per cent of those patients whose grafts closed during the first year Indeed proximal coronary arteries had progressed to occlusion in 30 per cent of one series of patients with grafts patent for one year

The presence of an apparently functioning graft does not preclude the progression of stenosis in the section of the artery distal to the anastomosis This has been reported in 8 per cent of one surgical group In that same series 13 per cent of patients revealed progression of atherosclerosis in non grafted vessels after one year

Obviously the underlying disease process atherosclerosis is not basically affected by these surgical interventions On the other hand alteration of the flow and hemodynamics of the vasculature by interposition of grafts has an effect on the stresses and responses of the affected coronary arteries A minimal existing process conceivably can be accelerated and earlier stenosis result from a combination of thrombotic and atherogenic factors This may even be augmented by increasing flow through the distal vessel beyond a critical point The high incidence of proximal arterial occlusion suggests that a preferential flow through the graft may cause a steal syndrome with deprivation of flow subsequent thrombosis and occlusion of these diseased arteries As yet there are no meaningful data regarding the mechanisms of these observations and further study is necessary

Conclusions

At the present time the operative mortality rate of aortocoronary artery bypass grafting ranges from less than 3 per cent to about 10 per cent More than half of these deaths are due to myocardial infarction Another 17 to 18 per cent of surviving patients may develop myocardial infarction during the year following operation

About 20 per cent of saphenous vein grafts fail to remain patent for one year Closure usually is associated with return of angina untoward change in clinical status and possible myocardial infarction Many physiological pathological and technical factors are relevant to graft patency Of prime importance is the establishment of blood flow of more than 40 ml per minute through the grafts and adequate size of the recipient artery at the site of anastomosis

Medial hypertrophy and subintimal fibrous hyperplasia of vein grafts the experimental greater durability of arterial grafts and the reported higher long term patency of internal mammary artery to left anterior descending coronary artery bypasses have stimulated current interest in the use of arteries rather than veins for grafting material In addition to direct internal mammary anastomoses to the left anterior descending coronary free arterial grafts and direct splenic artery bypasses have been utilized for left circumflex and right coronary artery bypass procedures

Progression of the underlying disease process atherosclerosis is not halted by these surgical technics Total occlusion of the coronary artery proximal to the site of graft insertion is extremely common regardless of whether the graft remains open or closed during the first postoperative year The recipient coronary artery distal to the anastomosis may stenose in a smaller number of patients about 8 per cent in one group restudied Atherosclerosis had progressed in non grafted coronaries after one year in 13 per cent The change

the number of undiagnosed areas of necrosis may be underestimated.

The incidence of operative myocardial infarction is significantly related to the severity of anginal symptoms, number of grafts inserted, and prolongation of heart-lung bypass pump time beyond two hours. Statistically significant differences were not apparent in regard to smoking, previous myocardial infarction, or abnormal lipoprotein profile.

During the year following surgery, late myocardial infarction unrelated to graft closure is difficult to document. Occasionally silent myocardial infarction can occur in the presence of patent grafts and a few patients may remain relatively asymptomatic despite occlusion of one or even all of the grafts. Usually graft closure is associated with dysrhythmias, return of angina, hypotension, a distinct deterioration in clinical status, and clear-cut new electrocardiographic abnormalities consistent with acute myocardial necrosis.

Patency of grafts

Clinical response of angina correlates well with graft patency. Very few patients remain completely asymptomatic in the presence of closed grafts. Early closure has been associated with lack of symptomatic improvement and occasionally with impairment of function. Recurring angina after initial relief, sudden arrhythmias, and transient hypotension can occur during the first postoperative year and may require early restudy to determine the adequacy of the revascularization procedure. Reoperation following clinical failure of bypass grafts may be feasible and necessary.

Loss of patency of inserted grafts remains a significant complication. In all series there is both an early and late closure rate which approaches 20 to 25 per cent within the first year. Many physiological, pathological, and technical factors have been implicated. In general, patency has been attributed to those grafts with favorable blood flow of more than 40 ml. per minute established at surgery and adequate caliber of the recipient artery with good distal runoff.

There is an inverse relation of flow to length and the cross-sectional area of the conduit created. Short, small caliber grafts have more rapid flow rates. An advantage of increased velocity of flow is to reduce the tendency for platelet and fibrin deposition and decrease thrombus formation.

Wall tension of the grafts is proportional to their length and to the size of the lumen. Greater tension is developed as the radius is increased and the grafts are elongated. In addition to the effects of enhanced tension in regard to possible development of medial hypertrophy of the grafts in the future, increased resistance may be a factor in thrombus formation within the grafts.

Coronary flow occurs predominantly in diastole. During systole, myocardial tissue pressure around small distal coronary arteries may reduce transmural pressure and temporarily occlude them, contributing to thrombus in traumatized grafts or inefficient anastomoses. Competitive flow between the proximal artery and a graft or even between different grafts and the presence of collateral circulation may jeopardize graft patency.

Although atherosclerosis has not been recognized, subintimal fibrous hyperplasia has developed in saphenous vein grafts. Reaction to stress of arterial pressure on the vein wall and a possible water hammer effect created by distal stenosis may be responsible. Other factors are ischemia of the vein and mechanical injury at the time of harvesting.

Problems with maintenance of functioning vein grafts have focused attention on the use of internal mammary artery anastomoses to the left anterior descending coronary artery. A 97 per cent long-term patency rate has been claimed. However, many of these patients required additional vein grafts to left circumflex and/or the right coronary arteries, only 70 per cent of which were found functional at the time of restudy. Furthermore, operating time is longer with its attendant higher complication rate.

The internal mammary artery has a relatively small diameter with an inherent high velocity, an aid to patency. On the other hand, it may not always provide adequate flow for distal arteries. The fact that arterial grafts experimentally have been more durable than vei[illegible] that the

Annotations

Whither electrocardiography?

The art or science whichever one prefers of electrocardiography is now some 60 years old Many advances have occurred since the pioneering studies of Einthoven and yet today lectrocardiography still has many limitations Reasons for this less than satisfactory state are such things as variations in body habitus from patient to patient the placement of precordial electrodes and the re ponse of the recording instrument—to name a few

The position of the precordial electrodes has been standardized by the British and American Heart Associations but in actual practice these positions are seldom accurately ascertained and certainly the positions are not reproduced accurately by technicians in the recording of daily electrocard ograms *It would obviously help to mark the* positions which were actually used by a dye or by silver nitrate *if multiple electrocardiograms are* expected to be taken In lieu of this a different positioning of the electrodes over the left precordium to encompass an area instead of a line would be of help This might include a high V_4 and V_6 lead with a V lead in the center like the five spot on a die

Let us consider the recording instrument The original string galvanometer as devised by Einthoven was a most satisfactory instrument provided the electrodes were properly applied to achieve low sk n resistance The response was linear from DC to several hundred cycles per second However the instruments tended to be bulky difficult for technicians to use and the strings were frequently broken The records required photographic process ng as well To get around some of these problems direct writing instruments using vacuum tube amplifiers and heated styli recording on heat sensitive paper were introduced some 30 years ago Instruments of this type have been improved by the use of solid state components and response electrical safety time decay and similar functions are better The fact remains however that salesmen technicians and even physicians can easily change the response of the instrument to provide cleaner records *by increasing the pressure of the record ng* stylus on the paper Thus the instrument no longer meets the *specifications* set by the manufacturer and supposedly met when the instrument was delivered to the consum r

In 1967 a special Committee of the American Heart Association[1] proposed minimal standards for electrocardiographic instruments This received some attention from the manufacturers and now a few companies produce in truments which meet some if not all of these minimal standards

Accuracy is of prime importance in the frequency range from DC (flat response) to perhaps 2 000 Hz but there is no universal agreement on these figures particularly the upper limit (A H A minimum standards call for a flat response from 0 14 c p s to 50 Hz with a 3 db falloff at 100 Hz) The higher the frequency response the more problems arise from 60 Hz interference and from muscle tremor and most studies in the high frequency range above 130 c p s have been limited to research investigations

There are however certain limiting factors in the direct writing electrocardiograph which make it less than an ideal instrument for accurate recording *of the electrocardiogram* These *include the mass* and inertia of the stylus and the friction of the *stylus on the paper* There will always be certain compromises which must be made between cost size accuracy ease of operation patient safety sensitivity to outside interference and the like

The low frequency response of the instrument (0 to 5 Hz) in view of today s knowledge is probably of equal if not greater importance Errors in the 0 to 5 Hz band are common due to paper friction or stiction and poor amplifier response to minute signals in this range This is especially important when one considers that probably 90 per cent of abnormalities noted in the electrocardiogram are confined to this range the P wave the P R interval the S-T segment the T wave and the U wave It is especially important to recall that repolarization is beginning in some cells even before the end of depolarization (QRS) and much information may be present in the S-T segment if it is accurately recorded

This brings us to the considerations of what may be done to improve the quality of direct writing electrocardiograms without unduly affecting cost and other factors mentioned previou ly

One way to improve low frequency accuracy by lessening the effect of paper stiction and stylus friction and amplifier distortions in the ± 0 1 mv range is to amplify the voltage and record at 2 to 20 times the normal standardization It is obvious that this will usually throw the QRS complexes off the paper which may damage the stylus or activate a protect circuit It is however possible using special circuitry to clip the QRS complexes and get accurate recording of the low frequency components (Fig 1) Accuracy in timing can be achieved

in hemodynamics and flow patterns within the coronary circulation provoked by the interposition of bypass grafts is complex and requires further study in order to understand any direct relationship to possible acceleration or deceleration of the basic occlusive arterial disease

These complications of aortocoronary artery bypass surgery are important determinants of postoperative morbidity and death They will influence the subsequent course of the patient and can change an excellent initial clinical response into an untimely death Better understanding of the mechanisms of these complications undoubtedly will help reduce their incidence in the future At the present time recognition of these events is necessary to afford the patient the best possible therapeutic management during the early and subsequent postoperative periods

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high frequency response with a flat response from DC to perhaps 2 000 Hz Paper speed should be faster and accurately timed Amplitudes should probably be increased at least in those leads with very low voltage There should be a built in testing system which can check the continuity of all leads the function of networks used in unipolar lead current leakage frequency response and decay times

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Aspirin in the prevention of thrombosis

It has been demonstrated that aspirin inhibits the platelet release reaction which suggests that the prolongation of the bleeding time by aspirin is probably but not necessarily secondary to this action

This finding raised the possibility that aspirin might prove valuable in some pathological conditions involving thrombosis The idea needed exploring in view of the enormous medical social and economic importance of thrombotic conditions in the Western world and it was decided that the *following trials should be carried out*

Before their selected operation and daily for five days thereafter 303 patients were given 600 mg of aspirin or a placebo in a carefully controlled double-blind study carried out in *four separate* hospitals The patients legs were scanned daily after the injection of ^{125}I labelled fibrinogen for hot spots which indicate local fibrin deposition i e a thrombus The result was clear cut A dose *of* 600 mg of aspirin has no effect at all on the incidence of hot spots during the first five postoperative days and the incidence of clinically detectable thrombosis was too low for a meaningful comparison but the few cases observed occurred equally *in the* treated and placebo groups[1] Although platelets are believed to play a vital part in blood coagulation the extent to which they are involved in the deposition of isotopically labelled fibrinogen in the legs is of course not known However it can now be deduced with certainty that the release reaction and any other changes brought about by aspirin play no part in the formation of these thrombi after operations

This is a strong assertion particularly in the present climate of opinion about the role of platelets in clinically detectable thrombotic disease and the widespread use of aspirin clinically to protect patients from thrombosis So the following points must be made

Aspirin has no effect on the primary wave of platelet aggregation—stickiness—induced *by adeno*sine diphosphate so this mechanism could still be involved in venous thrombosis detected by the ^{125}I labelled fibrinogen method used in the study This can be resolved only by finding compounds which interfere with this process and subjecting them to a similar clinical trial

Are the hot spots detected by the ^{125}I fibrinogen method a true reflection of clinical thrombosis? There is no doubt that the accumulation of fibrinogen in the leg veins does indicate a thrombus locally and this can usually be demonstrated by venography But there are certain important differences between thrombi detected by this method and the clinical disease we have known so long For example hot spots occur frequently (in up to 71 per cent of some prolonged operations) Furthermore they *are usually* small arise *in the* calf and are often found on the first postoperative day The vast majority *are clinically* silent and are associated with no known sequelae By contrast clinically detectable postoperative venous thrombi are usually recognized *later are found in* the thigh and of course occur much less frequently All the differences can be at*tributed* to the fact that only a small proportion of ^{125}I fibrinogen type thrombi extend along the veins *up into the* thighs where they are found later and much less frequently So that although the very great value of the ^{125}I fibrinogen test in research and *sometimes* in clinical conditions is accepted it is pertinent to ask if it is too sensitive on the one hand or whether the condition we need to investigate is a succession of events which occur subsequent *to the* deposition of the original thrombus When one considers the most serious complication of postoperative thrombosis pulmonary embolism *it is probably* true that the ^{125}I fibrinogen test would be positive in all cases even in patients with silent pulmonary thrombi but this does not explain why it is positive in such very large numbers of patients who remain free from all symptoms

It might be suggested therefore bearing in mind

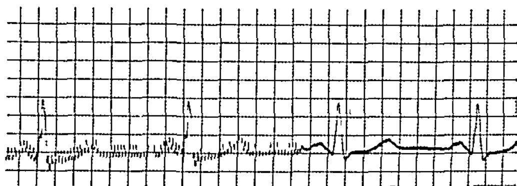


Fig. *1* Example of an electrocardiograph lead recorded at 50 mm per second paper speed. A 60-cycle notch filter was inserted into the circuit after the first two complexes and the almost complete rejection of 60 Hz interference can be seen without significant alteration in the electrocardiographic complexes. The short black lines at the top of the tracing indicate 1 second time intervals. The paper speed here is approximately 51 mm per second—an error of 2 per cent. This figure can be used for corrections if necessary. Thi is more important at speeds of 100 mm per second as used in recording systolic time intervals.

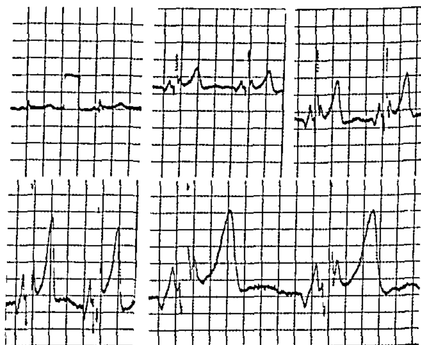


Fig. *2* The top left box indicates an electrocardiographic lead at normal standardization of 1 millivolt equal 1 cm. The top middle box is the same lead amplified three times, the top right box is the same lead amplified six times, and the lower left box has an amplification of ten times. The above were recorded at a paper speed of 25 mm per second as indicated by the one second time intervals at the top of the tracings. The lower right box is the same as the lower left (×10) except that the paper speed is 50 mm per second. Many details in the P, QRS, and S-T segment can be seen which are not readily apparent in the standard lead.

by recording at paper speeds of 50, 75, or 100 mm per second provided the paper can be moved accurately. A time marker must be simultaneously recorded to assure this accuracy. More paper is used but it is only necessary to record a very few complexes at fast speeds and high amplifications.

Another way in which the records can be improved is by the use of sharp notch filters since the greatest interference by far encountered is 60 Hz. This will change the height of the QRS complexes to some extent, but it is doubtful if this will really limit the diagnostic importance (see Fig. 2 with and without notch filter).

Other refinements consist in the recording of multiple simultaneous leads. This makes the interpretation of artifacts and arrhythmias much easier.

While there are other areas that could be mentioned, these points give an indication of the problems. As long as we accept the use of direct writing electrocardiography with the limitations inherent, it may be worthwhile to reconsider some of the concepts of "standards" such as electrode placement, paper speed, and amplification.

If it is really our intention to obtain the best possible recording of the electrocardiogram, then a suitable authoritative group should set standards of

connected peripheral portions depending upon the anterior subdivision the posterior subdivision and a central radiation or plexus of ramifications coursing to the midseptal area

These data were not entirely new Several older papers reviewed by Rossi reached similar conclusions *More recently* Medrano and associates[5] observed the same distribution of the left bundle fibers in the dog They also showed that it was possible to produce experimentally a concomitant block of both the anterior and posterior subdivisions without producing the classical pattern of left bundle branch block provided the midseptal ramification were not injured during the experimental procedure[5] Our results also fit in very well with the electrophysiological data obtained by Durrer and co-workers[6] who found that the excitation of the endocardial surface of the left ventricle simultaneously starts at *three widely separated areas* which may reasonably be assumed to correspond to the termination zones of the three main portions of the left branch In the light of these results the current concept which states that the left bundle branch is anatomically a bifascicular system appears tainted with over simplification

Let us now turn toward the histopathological lesions underlying the patterns of hemiblocks Recent observations indicate that it would be hazardous when one sees a tracing with LAHB or LPHB to draw hasty conclusions as to the precise topography of the partial bundle branch lesions responsible for the electrocardiographic abnormalities [7] In the above mentioned paper[3] we also reported on the histopathological features observed in ten patients with LAHB In nine out of 10 instances conspicuous alterations of the left branch were depicted They totally interrupted the anterior subdivision in five patients but were hardly ever limited to an anterior locus The pathological process generally involved most of the left sided conduction system Since this paper appeared several additional cases were studied they brought supportive evidence in favor of our initial opinion which is shared by Rossi[4] and Blondeau and Lenègre [8] We may therefore conclude that the patterns of hemiblocks are manifestations of left bundle branch disease but that the underlying *pathological lesions are generally much more widely* distributed than expected from the electrocardiographic terminology of left *anterior* or *posterior* hemiblocks

It is our belief that the problem of left intraventricular conduction disturbances should be reappraised Keeping in mind these histological data Indeed the validity of the term hemiblock which etymologically implies that the *bifascicular nature* of the left bundle branch system has been used as the unique basis for terminology should be questioned Similarly further basic and clinical studies are still needed to determine the actual role played by the *centro-septal fibers in the genesis* of both the normal and pathological QRS

The numerous papers that were devoted in *recent years to* partial left bundle branch blocks have opened a chapter which represents a most significant contribution to electrocardiology This chapter should not be considered as completed further work remains to be done in this field

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8. Lenegre J Personal communication

Pork and hypertension

Several years ago it was indicated that pork will produce arterial hypertension[1] This message has been ignored Careful medical histories usually reveal that patients themselves learn that eating pork will increase their blood pressure produce headaches of varying severity giddiness scotomata dyspepsia, pounding of the heart beat tinnitus and other symptoms and signs of rather sudden eleva

the marked difference between ^{125}I fibrinogen-detected thrombi and the clinically detectable disease that some additional hypothetical factor is necessary for the former to develop into the latter If this were so then it is highly probable that any treatment which prevented the formation of ^{125}I fibrinogen-detectable thrombi would also prevent the superimposed clinical disease But one could also argue at least theoretically that it might be possible to block the hypothetical factor necessary for the development of the full clinical picture without necessarily altering the incidence of ^{125}I detectable thrombosis

It is highly unlikely that aspirin would affect such a hypothetical additional factor and indeed the evidence is against it[1] nevertheless there are some who would argue that it would be desirable despite the discouraging findings in the present trial to carry out a further investigation involving very much larger numbers of patients to decide whether aspirin has an effect on clinical postoperative venous thrombosis or not particularly since one study has been reported claiming to demonstrate some clinical benefit from the administration of aspirin[3]

Clearly many factors both known and unknown contribute to the development of venous and arterial thrombosis Local precipitating abnormalities must be important in thrombus formation because venous and arterial systems as a whole never clot solid Platelets almost certainly play a far larger part in arterial thrombosis and it would seem rational indeed mandatory in view of the great importance of arterial thrombosis to evaluate the effect of aspirin in as many thrombotic situations as possible with a view to identifying those conditions where its specific effects have therapeutic benefit

There is already convincing evidence that aspirin is of real value in patients with amaurosis fugax[4,5]

One recognizes daunting logistic problems in organizing suitable trials especially in myocardial infarction which is a rare disease in terms of patient years Furthermore it will prove difficult to keep the control subjects from taking aspirin as it is now consumed on such a vast scale throughout the Western world Nevertheless we hope such trials will be pushed through to their logical conclusion despite the evidence that aspirin is without effect in postoperative venous thrombosis and we await the results of those trials already under way with keenest interest

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Left hemiblocks revisited from the histopathological viewpoint

The introduction of the concept of left hemiblocks[1,2] undoubtedly represented a fundamental step forward in the understanding of intraventricular conduction disturbances The assumptions which formed the basis of this concept were extremely useful especially for didactic purposes Nevertheless in course of time it seems that these assumptions deserve further attention in particular from the anatomical and histopathological viewpoints

It is for example generally agreed that the left branch is anatomically a bifascicular system which acts physiologically as such[3] We[4] recently had the opportunity to test this assumption in a histological study of the left bundle branch system carried out on 20 hearts from patients devoid of conduction defects This investigation confirmed the consistent presence of a thin and elongated anterior radiation and of a wider posterior one However in addition to these two well known fasciculi the left branch was observed to frequently give off a third radiation designated to cover the midseptal surface (11 out of 20 cases) This easily identified structure emerged either from the common left bundle (five cases) or from the anterior (three cases) or posterior radiation (three cases) In the remaining nine instances the septal coverage was supplied either by the posterior radiation (three cases) or by a complicated plexus of ramifications given off by both the anterior and posterior fasciculi (six cases) The anatomical features were such that in most cases it seemed reasonable to describe the left ventricular Purkinje network as composed of three main widely inter

Letters to the Editor

Digoxin tablets: A possible problem with biological availability

To the Editor

The Food and Drug Administration suggests that pharmacists keep for the information of physicians a record of the brand name and manufacturer or *supplier as well as the lot number* of all digoxin tablets dispensed.

In a recent editorial in the *Journal of the American Medical Association*[1] FDA affirmed the possibility of variance in digoxin tablets and recommended particular vigilance when patients obtain a new supply, whether made by the same or a different manufacturer.

FDA indicated that currently available information suggests the following:

1. Digoxin tablets from different manufacturers and suppliers may not be equally bioavailable; therefore may not be therapeutically equivalent.
2. If unexpected difficulty is encountered in digitalization with digoxin tablets, the physician should consider bioavailability as a possible source of the problem.

The physician should be alerted to these two points when evaluating the status of his patients, particularly at a time when they obtain a new drug supply, whether of a second brand or even the same brand, since the possibility of lot-to-lot bioavailability inconsistency cannot be ruled out at this time.

The FDA emphasized that if a bioavailability problem does exist with regard to tableted digoxin products, it is because we have become more sophisticated in our ability to define the factors that influence drug therapy, rather than any identifiable *change on the part of the industry*.

The Agency pointed out that the systematic testing and voluntary certification programs instituted by the FDA in 1970 to insure that digoxin tablets contain the specified quantity of active ingredient and meet *other compendial requirements* do not address the problem of bioequivalence and that additional studies are underway to determine whether an actual problem exists and to determine its magnitude if it does exist.

For readers who desire detailed information about the problem of bioavailability of orally administered digoxin as presently understood, several articles are *recommended*.[1-7]

Additional pertinent information on the subject, when it becomes available, will be published in the *FDA Drug Bulletin*. Physicians and pharmacists who are not now receiving the *Bulletin* may do so by writing:

Assistant to the Director for Medical Communications
Bureau of Drugs (BD 40)
Food and Drug Administration
5600 Fishers Lane
Rockville, Md 20852

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tions in arterial blood pressure The substance in pork responsible for these reactions remains unknown Some people are so sensitive to pork that mere traces of bacon grease or of pork seasoning in food are sufficient to increase arterial blood pressure to dangerous levels Daily use of pork in food will maintain elevations in blood pressure in patients with arterial hypertension Acute elevations in blood pressure will return to normal when the patients are placed on a pork free diet Elimination of pork from the diet of most patients with so-called essential hypertension will render the regulation of blood pressure not only possible but easy

The history of Mrs V S a 42 year old Negro woman illustrates the relation of pork intake to arterial hypertension This patient develops a rather sudden elevation in arterial blood pressure when she eats pork chops (her favorite meat) develops a splitting and unbearable headache blurring of vision marked giddiness pounding of her heart tinnitus and a feeling of being seriously ill and near collapse Her blood pressure increases to 240/140 or more at rest on occasions after eating pork for a few successive days These symptoms will last for hours and gradually subside if she abstains from pork All clinical manifestations of illness disappear and her clinical state returns to normal including her blood pressure without medication

This patient s 35 year old brother B M participated in a family feast in which a hog was killed and fresh pork was consumed in large quantities He suddenly developed a malignant type of hypertension (220/170) with hematemesis hematuria blood in his stools palpitation hyperhydrosis markedly impaired vision with the syndrome of hypertensive encephalopathy and coma and then died quickly

The magnitude of sensitivity to pork varies among people and the amount and days of consumption required to produce hypertension also vary among patients Some patients manifest no reaction whereas others have fulminating reactions as de cribed for the two patients above There is no doubt that a *complete* elimination of pork in all forms is a good dietary therapeutic rule in the management of arterial hypertension in all patients In addition the elimination of all forms of pork from the diet of all people may be a good practice for the prevention and the control of hypertension one of the most common and important illnesses of man Salted pork is even more hazardous to the health of man

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REFERENCE

1 Burch G E Phillips J H and Wood W The high pork diet of the Negro of the Southern United States (Editorial) A M A Arch Intern Med 100 859 1957

Books received

√

THE CLINICAL DELINEATION OF BIRTH DEFECTS Edited by Daniel Bergsma M D Baltimore 1972 The Williams & Wilkins Company 325 pages Price $29 00

√ CARDIOVASCULAR PHYSICAL DIAGNOSIS Edited by Martin J Frank M D and Sergio C Alvarez Mena M D Chicago 1973 Year Book Medical Publishers Inc 186 pages

CLINICAL SCALAR ELECTROCARDIOGRAPHY Edited by

√ Bernard S Lipman A B M D F A C P F A C C Edward Massie A B M D F A C P F A C C and Robert E Kleiger B A M D Chicago 1972 Year Book Medical Publishers Inc 721 pages

√ AN ABC OF MODERN IMMUNOLOGY By E J Holborow M D Cantab M R C P M E C Path Boston 1973 Little Brown & Company 94 pages Price $4 95

Book reviews

Chronically Implanted Cardiovascular Instrumentation Edited by Ernest P McCutcheon New York and London 1973 Academic Press Inc 482 pp Price $14 50

This book on the proceedings of a symposium held in Lexington Kentucky during October 17 to 20 1971 on implanted cardiovascular instrumentation should interest physiologists and others studying cardiovascular physiologic phenomenon The many contributors and contributions review extensively the many problems of instrumentation techniques data analysis and application of implanted devices to study cardiovascular physiologic phenomenon Even though this book will not interest clinicians the problems under study eventually will have clinical significance Engineers physicians bioengineers and biophysicists as well as physiologists will find this book to be extremely valuable The reviews of techniques and application reveal the many complex and important cardiovascular problems yet to be studied This is a good and important publication

Cardiac Arrhythmias The Twenty Fifth Hahnemann Symposium Edited by Leonard S Dreifus, M D and William Likoff M D New York 1973 Grune & Stratton Inc 681 pp Price $29 75

With great interest in arrhythmias these days this publication of the papers presented at the 25th Hahnemann Symposium should interest all cardiologists and internists The many contributors review the arrhythmias for the reader Of course it contains nothing new but anyone who wishes to study arrhythmias will find this to be a valuable publication This publication brings up-to-date the discussions of the 14th Hahnemann Symposium on arrhythmias of 7 years previous This book is recommended for the clinician Like the previous publication on arrhythmias this volume is presented from a practical point of view

American Heart Journal

December 1973, Volume 86 Number 6

Acknowledgment to reviewers

The Editors wish to express their thanks and appreciation to the following who have aided in the review of manuscripts during the past year

F M Abboud
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Announcements

Cardiology symposium

The University of Texas Health Science Center at Houston Division of Continuing Education will present a Cardiology Symposium on December 3 through 6 1973 at Houston Texas This program will present an intensive review in cardiology The guest lecturer will be James J Leonard M D Professor and Chairman Department of Medicine School of Medicine University of Pittsburgh Pitts burgh Pa

For further information write The Office of the Director The University of Texas Health Science Center at Houston Division of Continuing Educa tion P O Box 20367 Houston Texas 77025

Eleventh Annual Cardiology Seminar

The Rogers Heart Foundation announces the eleventh annual Cardiology Seminar under its spon sorship to be held at the Princess Hotel South ampton Bermuda on December 6 through 9 1973 The seminar theme is Coronaries and Contro versies Program director is Henry J L Marriott M D Faculty are Dr Agustin Castellanos Miami Dr Robert Eliot Omaha Dr Desmond Julian Edinburgh Dr Frank LaCamera Jr St Peters burg Dr Harold Mankin Rochester Dr Henry J L Marriott St Petersburg Dr Victor Parson net Newark Dr Joseph Reeves Birmingham and Dr Leon Resnekov Chicago

For further details please write Rogers Heart Foundation St Anthony s Hospital St Peters burg Fla 33705 Telephone (813) 894 0790

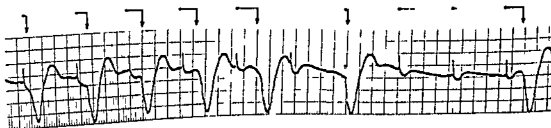
Annual meeting of American Thoracic Society

The Annual Meeting Committee American Tho racic Society Medical Section of the American Lung Association invites submission of papers on all scientific aspects of respiratory disease for pres entation at the 1974 annual meeting in Cincinnati Ohio May 12 through 15 1974 Membership in the Society is not a prerequisite to participation in the program Abstracts of papers should be submitted to the Chairman of the Annual Meeting Committee before January 15 1974 Abstracts of papers from investigators outside the United States will be wel come provided they are in English and are sub mitted with the understanding that all papers ac cepted must be presented clearly in English at the Annual Meeting

Required forms and instructions may be obtained by writing Joseph F Tomashefski M D Chair man Annual Meeting Committee American Tho racic Society 1740 Broadway New York N Y 10019

Erratum

In the August 1973 issue of AMERICAN HEART JOURNAL in the article Mechanisms of cardiac arrhythmias From hypothesis to physiologic fact by Dr Alfred Pick Fig 35 on p 266 was inadvertently reversed The correct figure is illustrated below



Editorial

An assessment of human cardiac transplantation

*A Moneim A Fadali M D**
*Louis A Soloff M D***
Philadelphia Pa

On August 24 1972 Louis B Russel Jr an Indianapolis school teacher celebrated the fourth anniversary of his heart transplant No one else has lived so long after heart transplantation[1] His four year-old heart used to belong to a seventeen year-old boy from Providence Forge Virginia who was killed while stepping out of a restaurant during a ghetto fight[2] Lower and his team performed the operation at the Medical College of Virginia This outstanding achievement and the recent reports from Shumway s group[15,34,54] at Stanford University make it important for those of us not actively participating in cardiac transplantation to take stock of what has been accomplished by and what has been learned from this operation This knowledge is important to assess the place of cardiac transplantation in the over all management of the grossly disabled cardiac patient

Transplantation of organs and tissues intrigued the imagination of mankind since antiquity The Iliad[3] thus described a chimera

> A mingled monster of no mortal kind
> Behind a dragon s fiery tail was spread
> A goat s rough body bore a lion s head
> Her pitchy nostrils flaky flames expire
> Her gaping throat emits infernal fire

This mythical monster after devastating Caria and Lycia was killed by Bellerophon mounted on his winged steed Pegasus The word chimera has recently been introduced into medicine to describe an animal which possesses for a long time viable cells from another animal

The chimera was for centuries a figment of the imagination and the adjective chimerical became synonomous with imaginary Nonetheless the universal significance of this concept is attested by its persistent influence on the arts of many civilizations from antiquity to the present day Except for minor procedures on the face nose and penis the ancients had to be satisfied with prostheses The Talmud[4] records the use of crutches artificial limbs and teeth procedures that were practiced by other civilizations before and at that time The increased need for prosthesis during the two world wars combined with the constantly developing industrial revolution led to the introduction of many sophisticated and electrically controlled prostheses which could simulate the movements of almost all voluntary and many involuntary groups of muscles including the fine movements of the thumb and fingers All of these prostheses were applied to the

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external surface of the body. Except for a few botanical[5] and dental procedures, a rare bone, thyroid, and experimental kidney transplant,[6,7] internal prostheses and chimerical operations had to await the development of a variety of apparently unrelated techniques and the recognition of their applicability to medicine. Some of these techniques are instruments for cutting, anatomic dissection, experimental physiology, anesthesia, antisepsis, roentgenology, blood and tissue typing, heparin, and cellophane, all eloquent testimony to the unanticipated dividends of basic and industrial research to the welfare of mankind.

We cannot resist speculating on the future of the artificial heart because its future will, we think, greatly influence the usefulness and perhaps the practice of cardiac transplantation. Of all the internal organs, the heart, arteries, and veins appear the most likely candidates for prosthetic replacement. This is so because the vital function of the heart is to act as a pump and that of the arteries and veins to convey blood. Pipes and pumps are well known products of industry. There is no difficulty in making and energizing a pump powerful enough to propel the amount of blood adequate to meet the needs of the body and in making a pipe strong enough to withstand the flow of blood. That the blood could tolerate so well a large clumsy foreign body like the Starr-Edwards valve was an astonishing revelation. This success helps to sustain our faith in the ultimate development of a successful artificial heart. At the present time, Kolff[8] states that the limiting factors for total cardiac replacement are thrombosis, hemolysis, and right heart failure. Dogs with an artificial heart have lived as long as eight days. From the standpoint of survival, these dogs are equivalent to Mann and colleagues'[9] dogs with transplanted hearts in 1933. We have every reason to believe that continued collaboration between biological and physical scientists with adequate facilities and financial support can solve this important problem in less than the 35 years that elapsed between Mann's experiment and the first successful human cardiac transplantation. Such an achievement would be of immense importance. It would solve the problems of supply and immunologic complications, two main obstacles hindering practicability of cardiac transplantation, and would also obviate some difficult and distasteful ethical questions. At the present time, from the standpoint of survival, the artificial heart is not a reality. Cardiac transplantation is.

Carrel and Guthrie[10] in 1905 transplanted a heart to the neck of a dog. The heart beat spontaneously for one hour. Using the same model, Mann and associates[9] in 1933 reported survival periods up to eight days with normal heart beats. Faced with a patient in terminal heart failure and with no suitable human donor available, James D. Hardy[11] of Jackson, Mississippi, transplanted the heart of a large chimpanzee to the dying patient on January 23, 1964. The transplanted heterograft maintained a blood pressure of 80 to 90 mm. Hg for approximately one hour. The first human heart homotransplant was performed by Christian Barnard[12] of South Africa on December 3, 1967. This accomplishment aroused intense controversy varying from absolute praise expressed by J. E. Edwards,[13] President of the American Heart Association, who called the procedure "A courageous and new advance in cardiology and a milestone in the history of medicine and surgery," to utter condemnation and anger expressed by the Nobelist Wilhelm Forssmann,[13] who compared heart transplantation to some of the Nazi experiments on humans. Enthusiasm was contagious and in the following year a total of 101 heart transplants were performed in several countries. Enthusiasm waned the following year because of the unacceptable mortality rate and possibly also for ethical and legal reasons. As of August 1, 1972, 194 heart transplants have been performed in 21 countries by 61 teams (Table I). At least two of these patients had combined heart and lung transplantation because of associated severe pulmonary hypertension in one and advanced chronic obstructive pulmonary disease in the other.[14] Two other patients underwent a second transplantation due to chronic rejection and graft failure after ten and seven months but both died in the early postoperative period.[14] Twenty-seven recipients are current survivors from two to 48 months after

*Table I Human heart transplantation—Chronology and world distribution (Dec 3 1967 to Aug 1 1972)**

Year	World totals	U S A	Canada	France	South Africa	Other countries
1967	2	1	0	0	1	0
1968	101 (7)†	54 (4)	14 (2)	10 (1)	2	21
1969	47 (3)	34 (2)	1	0	4 (1)	8
1970	17 (5)	16 (4)	1 (1)	0	0	0
1971	17 (7)	13 (6)	1	0	3 (1)	0
1972‡	10 (5)	8 (5)	0	0	1	1
Total	194 (27)	126 (21)	17 (3)	10 (1)	11 ([illegible])	30

*American College of Surgeons/National Institutes of Health Organ Transplant Registry
†Number in parentheses indicate survivors.
‡Data not yet complete

*Table II Human heart transplantation—Prolonged survival**

	> 6 mos	> 1 yr	> 2 yr	> 3 yr	> 3½ yr
Total recipients 191	49	36	21	11	9
Current survivors 27 as of Aug 1 1972	24	19	14	9	7

*American College of Surgeons/National Institutes of Health Organ Transplant Registry

transplantation nine of them living over three and one half years (Table II) The majority of the transplants were performed with ischemic cardiac arrest of the donor s heart according to the technique standardized by Lower and associates[15] Operative deaths were extremely rare and most of the mortalities occurred in the first three months after surgery The attrition rate declined sharply after the third postoperative year The over all six month one year two year three year and three and one half year survival rates are presently 20 per cent 17 per cent 11 per cent 5 7 per cent and 4 7 per cent respectively The group at Stanford University California headed by Dr Norman Shumway who have dedicated themselves to the study of this problem obtain much better results The over all survival rate in their series was 37 per cent at one year and 26 per cent at two years[14] The results of this group show steady improvement In 1968 22 per cent of their transplant patients survived one year whereas 50 per cent of those operated upon in 1970 to May 1971 survived at least one year[16] Almost all the long term survivors had achieved impressive degrees of physical social and vocational rehabilitation It is therefore clear that patients can survive cardiac transplantation and improve sufficiently to lead a useful life Indeed in the hands of the experienced cardiac surgeon the operative procedure no longer significantly limits survival However the percentage of patients who improve sufficiently to lead a useful life for an appreciable length of time is still disappointingly small

At first a great deal of effort was spent on determining whether the cardiac transplant could be re innervated and if not on the denervated heart capacity to perform work This is surprising in view of a classic experiment performed by Patterson Piper and Starling[17] in 1914 They showed that the denervated isolated heart possesses an intrinsic mechanism by which it can meet the demands of increased pressure and volume Casser and Meek[18] in the same year and Samaan[19] in 1935 did produce evidence that the dog s ability to exercise

was impaired by denervation Their experiments were criticized by other observors[20] who showed by employing similar techniques that other organs were also denervated and this may have altered the results Finally Donald and Shepherd[1,2] demonstrated that the Frank Starling mechanism was operative in dogs with chronic cardiac denervation Blinks[3] demonstrated that in the isolated heart distension of the right atrium had a positive chronotrophic effect in several animal species However Donald and Shepherd[4] could not find a linear correlation between increments of right atrial pressure and rises in heart rate in dogs with chronic denervation The most plausible explanation for the increase in heart rate and at least part of the increase in cardiac output is the action of circulating catecholamines[6] Denervation depletes the myocardial stores of catecholamines[27] and this renders the heart more sensitive to the action of circulating catecholamines This can explain the observed faster heart rate of the allograft heart at rest in comparison to control subjects The catecholamines released during exercise will also be effective In one patient[28] several months after heart transplantation measurement of the blood level of epinephrine and norepinephrine during exercise showed significant rise synchronous with the observed increase in heart rate Actually immediately after operation the heart resumes function either spontaneously or after electrical stimulation

There is over all agreement on the hemodynamic observations after human cardiac transplantation The reports from Shumway s group[9] are the most impressive because their findings were obtained one and two years after operation and while their patients were clinically stable

In essence at rest the heart rate is slightly faster than normal and not responsive to respiration the intracardiac pressure is normal, the cardiac index is low normal or just below normal the stroke index is slightly below normal and the arterio venous oxygen difference is slightly greater than normal This last form of failure suggests that the patient would not be able to tolerate exercise for long if at all which is maximal for the normal Indeed, this group found that arterial blood analysis during sub maximal exercise showed evidence of anaerobic metabolism at relatively low work loads and levels of oxygen uptake This occurs even though the ratio between an increase in cardiac output and an increase in oxygen uptake during exercise remains normal

During exercise the left ventricular end diastolic pressure rises abruptly the heart rate increases slowly to a plateau and after exercise it takes 20 minutes or more to reach its resting level The cardiac output increases without a significant change in left ventricular ejection time and the arteriovenous oxygen difference increases inordinately The systemic and left ventricular pressures rise progressively for the first few minutes of exercise and then reach a plateau for the remaining five minutes of exercise

It is noteworthy that the pulmonary artery pressure and resistance after transplantation can be close to normal That this is not always true is indicated by two of the first ten deaths reported by this group

The precise causes of the hemodynamic abnormalities are uncertain Unfortunately the chronologic clinical history of each patient is not given in most reports Although at least some of these findings resemble those in the canine denervated heart and in the chemically denervated human heart one cannot exclude the effects of increased afterload chemotherapy used at the time of study and the effects of rejection most likely present at least in the past The last effects are suggested by the marked deterioration at two years of one patient who at that time revealed severe diffuse narrowing of all the major coronary arteries with complete obliteration of the proximal left circumflex artery Such arterial changes can occur without clinical evidence of rejection It is this rejection phenomenon and the untoward effects of treatment aimed at preventing and reversing it that pose the stumbling block that must be removed before cardiac transplantation can pass from an experimental procedure to a clinically acceptable method of treatment

The rejection reaction is not related to the recipient s type of heart disease Similar lengths of survival have been reported

after operations on patients with cardiomyopathy congenital rheumatic and coronary heart disease and even in one patient with rheumatic heart disease and pulmonary artery pressure at systemic levels Transplantation therefore appears to be equally suitable for all types of heart disease and would be contraindicated only in those patients with extracardiac disorders that seriously limit life and also by absolute biologic incompatibility Finally none of the above dysfunctions of the transplanted heart have been of a sufficient magnitude to preclude a useful life and therefore would not be of any significant concern if further deterioration did not occur

Unfortunately present day methods of diagnosis and treatment have not been able to prevent the development of the rejection reaction Absolute contraindications to the use of a donor s heart for a particular recipient are (1) ABO blood group incompatibility (2) preformed antibodies in the recipient s serum to donor s lymphocytes and (3) gross disparity in the size of the donor s and recipient s hearts Rejection has occurred in the absence of other demonstrable incompatibilities and survival has been reported in instances with gross mismatches [30] These results suggest the likelihood of unrecognized factors such as chemically impure antigens and specific tissue loci not manifested by present day serologic tests Dr Amos of Duke University and Dr Bach of the University of Wisconsin[31] have recognized such leucocyte-defined loci and hopefully a practical test for their clinical recognition will be forthcoming in the near future In the meantime common sense dictates a choice of a donor with minimal antigenic disparities for a specific recipient

As long as the rejection reaction cannot be prevented the best way to cope with the situation is to detect it early and to treat it properly with agents that have the least untoward effects Such agents are also used with the hope of preventing postponing and attenuating the rejection reaction

Early detection is suggested by electrocardiographic (ECG) evidence of decreasing voltage atrial arrhythmias and rightward deviation of the QRS complexes [10] In some patients the appearance of a diastolic gallop was the first sign of rejection preceding the ECG changes [32] DeBakey and colleagues[33] reported that symptoms of anorexia and malaise can also precede ECG changes by 8 to 16 hours

Roentgenologic and ultrasonic evidence of increasing thickness of the left ventricular wall increased size of the right ventricle and the whole heart and changes in cardiac contractility have all been helpful [32] Clinical signs of cardiac insufficiency and the rise in enzymes (CPK LDH) are usually late signs of rejection More recently the Stanford group[34] has been doing endocardial biopsies on their patients to obtain baseline data with respect to the expected changes in the event of smoldering and chronic rejection

Evidence is accumulating that immunologic abnormalities precede and are more specific than all other evidences of rejection and can be used as a guide to intensify treatment with the hope of preventing clinical disability One method consists in serial measurements of serum titers of fluorescein tagged anti IgG globulins They are bound primarily to the sarcolemmal sheath of the myofibers [35] Another method is serial quantification of the level of inhibition of the conversion of C_3 [36] A third method is serial determination of the rate of spontaneous transformation of blood lymphocytes to blast cells in culture [37] These methods appear more sensitive than myocardial scanning with 131 cesium [38]

Azathioprine (Imuran) and prednisone are the drugs universally accepted for the prevention and treatment of rejection The doses initially must be high yet carefully regulated because both drugs enhance susceptibility of the host to pathogenic and opportunistic organisms The effectiveness of other methods of treatment has not as yet been established

Most recipients have received antilymphocytic globulin (ALG) or a purified globulin preparation from horse antihuman thymocyte serum for several weeks or months after operation Controversy concerning their value may be related to the development of antibodies against the foreign protein and the fact that these globulins are eliminated from the circulation 8 to 12 days after treatment [33] Nonetheless a

short term course may be of value in an emergency, particularly when leucopenia and hepatic dysfunction might contraindicate the use of Actinomycin D and increased doses of Imuran. There is evidence that ALG might enhance tumor growth.[39] Mice given ALG could not develop immunity to a second implant of sarcoma 180. However, none of the animals developed a spontaneous tumor.[40] At the Cleveland Clinic[40] 65 out of 200 recipients of renal transplants were given intramuscular injections of horse anti human ALG. In one case a reticulum cell sarcoma developed at the site of the intramuscular injection of ALG. However, the possible ALG potential for induction of neoplasia does not at this stage justify discontinuing this agent in the treatment of rejection.

Another method of treatment is based on findings in rats after skin allografting.[41] During periods of rejection it was found that the urinary histamine excretion was increased and also the histamine forming enzyme histidine decarboxylase activity in the allograft increased by 33 fold during rejection. Administration of histidine decarboxylase inhibitors prolonged the survival of skin allografts between inbred rats and suppressed the formation of antibodies to antigens.[41] The best results were achieved when semi carbazide a diamine hydrazide was combined with a pyridoxine deficient diet.[41] A close chemical relation exists between semi carbazide and isonicotinic acid hydrazide (INH). This group at UCLA Harbor General Hospital has added INH and histadyl H an antihistamine to the standard regimen of Imuran and prednisone. The program was started at operation in four renal and one heart transplant patients. None of them showed evidence of acute rejection up to six months after operation despite the fact that all were Terasaki C or D matches.

Local graft irradiation which has been found valuable after experimental and clinical renal homotransplantation is an attractive idea because it circumvents the systemic side effects of immunosuppressants. Irradiation injury to the myocardium is probably unlikely because the suggested doses are comparatively low. However, an underlying immunologic injury might enhance irradiation injury. The value of local graft irradiation after canine cardiac allografting has been shown by Graham and associates.[42] In 60 per cent of the animals serial myocardial biopsies showed striking histologic improvement when local radiation was employed to modify acute rejection episodes. The mechanisms involved are not entirely clear. The efferent arc of rejection might be interfered with through destruction of the lymphocytes which are known to be radiosensitive.[43] There is also evidence that the efferent arc or sensitization of the host might be impaired by graft irradiation.[44] Improved graft perfusion has been noted after irradiation due to amelioration of tissue edema associated with rejection.

The role of the thymus has been fascinating to those involved in organ transplantation. The cell mediated immune response rests on the longlived small lymphocytes. They are known to be thymus dependent. After a mysterious voyage from the bone marrow to the thymus gland, the small lymphocytes become immunologically competent.[45] Despite this crucial role of the thymus its removal at the time of transplantation apparently did not improve graft survival in clinical experience.

Perhaps the most successful approach to the problem of organ rejection will be the induction of immunologic enhancement.[46] Immunologic enhancement means the prolongation of allograft survival by the presence in the recipient of an alloantibody directed against the alloantigens of the donor's graft. The process may be accomplished by active immunization of the graft recipient with donor tissues or passively by administering to the recipient serum containing alloantibodies. This alloantiserum is prepared by immunizing another individual. It is not xeno or heteroanti serum as is the case with ALG. The alloantibodies by destroying or blocking the graft antigens will eliminate the destructive cellular responses to the graft antigens and therefore graft survival is prolonged. The greatest advantage of immunologic enhancement is its specificity. It does not increase the recipient's susceptibility to infection or malignancy as noted with modalities that are used to induce immunologic tolerance such as immunosuppression and radiation.

The best results were achieved when active and passive immunization were combined

According to Nossal[47] if the rules govern ing the activation of killer cells versus anti body forming cells could be described one can guarantee tilting the balance both in cancer and in transplantation

All these measures are most effective in suppressing the early rejection phenome non This early rejection is characterized anatomically by edema endothelial swell ing sloughing and inflammatory changes However these changes are not always manifested clinically and by present labora tory tests Furthermore clinical reversi bility does not exclude permanent anatomic damage Shumway[29 30 32] agrees that the separation of reversible from irreversible morphology during rejection is not clear This chronic form of rejection is not re ponsive to the measures listed above It is characterized anatomically by intimal proliferation with obliterative coronary ar tery disease and can begin as early as nine days after operation and be completely silent until gross and irreversible myocar dial dysfunction occurs Thus in three patients whose grafts showed the most severe signs of rejection numerous ECG s taken at rest and during exercise ballisto cardiograms ultrasonic cardiograms and other tests failed to be diagnostic of rejec tion Therefore it may be assumed that the usual immunosuppressive drugs were not effective in preventing this serious compli cation

More recently Shumway and colleagues[48] have reported normal coronary arteries as visualized by coronary arteriography in three patients studied one year after opera tion This group attributes the good success in the e patients to the use of a low choles terol low saturated fatty acid diet and to the use of warfarin and dipyridamole orig inally suggested by Kahn and associates[49] and by Kincaid Smith [0] These *findings* are extremely encouraging but their sig nificance is not clear because there was no change in the blood cholesterol coronary arteriography does not exclude gross ath erosclerosis and the time interval is too short This group had already shown that one cannot predict what changes will occur at two years based upon the findings at one year after operation Finally the dele terious effect of residual pulmonary vascu lar disease on the function of the right ventricle may explain predominant right heart failure after cardiac transplantation

Kosek and associates[51] state that graft atherosclerosis resembles spontaneous ath erosclerosis and any differences between the two can be explained by the differences in rates of development of the atherosclerosis This would suggest that spontaneous ath erosclerosis is an autoimmune disease Such a possibility is supported partly by Beau mont s[52] finding that hyperlipoproteinemia may on occasion be due to an autoimmune response It should be remembered how ever *that the number of ways that a tissue* can respond to injury is limited whereas the number of injurious agents is limitless We have not had the opportunity of exam ining graft atherosclero is Acute rejection is described as involving capillaries vaso vasorum veins and large vessels of the coronary arterial system The chronic form is characterized by major involvement of the first branches of the intramyocardial portion of the coronary arteries and a tre mendous proliferation of the intima These findings do not appear to us to resemble spontaneous atherosclerosis

Even after the rejection reaction will have been conquered other major problems relating to cardiac transplantation remain One is logistics relating to procurement and storage of cardiac allografts Organ banks are badly needed for prolonged storage Short methods of preservation are also required to reduce the inevitable ischemic damage which occurs preterminally before removal of the heart from the donor and which continues until graft revasculariza tion by the host Various methods have been employed to preserve the heart in a viable state These include hypothermia hyperbaric oxygenation freezing meta *bolic inhibitors* interim perfusion and the use of intermediary hosts Moderate hypo thermia is known to enhance organ via bility Deep hypothermia frequently leads to interstitial edema which may interfere with organ function after transplantation Kondo and colleagues[53] resuscitated canine hearts after 24 hours storage in saline at 4 C Lower[54] successfully homotrans

short term course may be of value in an emergency, particularly when leucopenia and hepatic dysfunction might contraindicate the use of Actinomycin D and increased doses of Imuran. There is evidence that ALG might enhance tumor growth.[39] Mice given ALG could not develop immunity to a second implant of sarcoma 180. However, none of the animals developed a spontaneous tumor.[40] At the Cleveland Clinic[40] 65 out of 200 recipients of renal transplants were given intramuscular injections of horse anti-human ALG. In one case a reticulum cell sarcoma developed at the site of the intramuscular injection of ALG. However, the possible ALG potential for induction of neoplasia does not at this stage justify discontinuing this agent in the treatment of rejection.

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18 years of age or older may donate all or part of his body for medical purposes to take place after death This can be spelled out in a uniform donor card In its absence the next of kin may act Legislation adopted in Kansas[66] has spelled out the time of death as that time after all resuscitative measures have failed when there is either absence of spontaneous respiratory and cardiac function or an absence of spontaneous brain function The ideal donor is one whose heart is still beating after spontaneous brain function has ceased It is now agreed that the electroencephalogram should be flat for at least two hours in the normothermic patients and should not be one that is depressed by drugs The act also provides that the time of death should be determined by physicians who attended the patient or who certified his death but these physicians cannot be those involved in removing and transplanting the part We would add that death should be certified by a neurologist or neurosurgeon and by the electroencephalographer

We hope that this definition of death will *not* discourage research on methods to revive an apparently dead brain After all it was not so long ago when ventricular fibrillation and cardiac standstill were regarded as irreversible signs of death Death of tissue is due to two independent and interacting factors *primary cessation of* anabolism and secondary impairment and cessation of anabolism by a hostile environment Obvious hostile environments are freezing and drugs The catabolic effects of anabolism if not removed can by themselves choke and kill cell These examples should *encourage* search for methods of determining the initial causes of *brain* damage and methods for reviving the brain

Because of the frequency of *occult* coronary artery disease the donor should *preferably* be a young adult

Who should be the *recipient?* It is a platitude to say that he should be *the one* who needs the heart most provided he has no other disorder that would *limit the* anticipated benefits from *the transplant* and provided he and preferably his family understand and accept the risks *involved* The question however is not so simple because prognosis particularly for the immediate future of those with coronary heart disease is not easy to define and because the demand far outstrips supply The Shumway group[18] is to be congratulated on the excellence of their diagnosis and prognosis The average survival rate of 20 patients whom they selected for transplantation but could not be operated on for various reasons was 30 days Half of them died by the tenth day after selection and only one patient lived more than 95 days This survival rate is significantly lower than that of transplant recipients at the same institution

It should be mandatory to preserve a chronologic detailed history findings and treatment of all patients who are being considered for transplantation Preference should be given to the younger patient but otherwise the physician should not try to judge the value of the life he hopes to save

Considering all these unsolved problems is the operation worthwhile? We agree with Claude Bernard[67] who a century ago defined the limits of human experimentation

It s our duty and our right to perform an experiment on man whenever it can save a life cure him or gain him some potential benefit The principle of medical and surgical *morality* therefore consists in *never* performing on man an experiment which might be harmful to him to any extent even though the results might be highly advantageous to science that is to say to the health of others But performing ex*periments and operations exclusively from* the point of view of the patient s own advantage does not prevent their turning out profitably to *science* [67]

Who then should perform the operation? We agree with Nossal[17] that the research *with respect (to cardiac transplantation)* should proceed cautiously remaining the province of the small number of groups with a profound commitment [17] These groups should be composed of scientists whose major research interest is in transplantation They should have adequate institutional facilities and paramedical help *All* persons engaged in this endeavor should be adequately supported so that if necessary they can devote their full time to the care of the patients There should be no charge whatsoever either personal institutional

planted a dog heart after a hypothermic anoxic period of seven hours. Using hyperbaric oxygen at three atmospheres in conjunction with hypothermia, the dog's heart was preserved up to 72 hours in a viable condition. However, Lyons and associates[56] achieved the same result with hyperbaric helium or nitrogen at three atmospheres, suggesting that pressure probably acts by inhibiting metabolism and preventing tissue edema.

Various methods and solutions have been used for perfusion with and without hypothermia in order to maintain organ viability. Methods utilized varied from the simple Langendorff columns[57] and the pulsatile perfusion system of Carrel and Lindbergh[58] to the elaborate heart-lung preservation chamber designed by DeBakey and associates.[59] Crystalloid and colloid solutions, plasma, and whole blood were used, and a long list of additives was frequently recommended: insulin, hydrocortisone, magnesium sulfate, penicillin and other antibiotics, tris buffer, and heparin—to mention a few. High osmolarity of the perfusate and hyperbaria were found beneficial to prevent edema formation. However, in any artificial system the perfused organ after a variable number of hours showed increased vascular resistance manifested by a rise in perfusion pressure, falling venous output, and increasing edema.[60] Metabolic and functional deterioration subsequently became apparent. The duration of organ viability with artificial perfusion has not been firmly determined. With the present status of perfusion, we think that 48 hours of organ preservation is a maximum beyond which successful organ transplantation would be highly unlikely. This period of time would allow functional evaluation of the preserved organ, tissue typing, and transportation of the heart to a recipient, and perhaps immunologic enhancement by perfusion with specific antibodies.

Organ preservation by freezing has been unsuccessful so far. During standard slow freezing, that is, about 1° C per minute, extracellular ice crystal formation occurs. Water is withdrawn from the cells to the extracellular ice crystals. Intracellular osmolarity rises and cellular injury results. To solve this problem, cryo-protective agents and super cooling have been proposed. Cryo-protective agents,[61] such as dimethylsulfoxide and glycerine, tend to inhibit extracellular ice formation and therefore to decrease cellular dehydration. However, these agents penetrate into the cells at a much slower rate than water and therefore during thawing osmotic damage to the cells might occur. With fast or super cooling, intracellular ice crystal formation occurs and cell survival declines. Apart from these problems, the main obstacle to freezing whole organs is that each population of cells has its own specific velocity of cooling. An optimum velocity for one kind of cell might be harmful to another kind.

Metabolic inhibitors were shown to prolong organ viability to at least double that of control organs.[62] The most promising metabolic inhibitor is 2 per cent magnesium sulfate. In addition to slowing the metabolic rate, it maintains membrane integrity and transmembrane potentials.[63] Intermediary transplantation in a temporary host has been suggested as a method of organ preservation by Angell and Shumway.[64] These hearts were shown by Wells and associates[65] to maintain an adequate *pump function after a period of seven* weeks. However, possible rejection from two hosts might undermine the usefulness of this method.

A number of moral and ethical issues related to organ transplantation must be resolved in the minds of those who are involved with the procedure.

In the present state of the art of organ preservation, the best chance of successful cardiac transplantation is the use of a donor heart that is still beating or has just stopped beating. However, we should all heed these wise words of Giertz: "A person dying is still a person living and he keeps his elementary human rights up to the moment when life is extinct."[66] There is a steady progression from clinical death to electrical (heart, brain) death to biologic death and then to cellular death, which is temporally different in different parts of the body. When the brain is totally dead, integrative vegetative life ceases with permanent extinction of body life.

The uniform anatomical gift act provides that any person of sound mind and

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or insurance to the patient It is unlikely that such conditions can be met without adequate federal support

Is the procedure worth this tremendous burden particularly the financial one at a time when most of our health institutions are in deep financial troubles? We elect to let Sir Peter Medawar[68] answer this last question "I sometimes think there is an almost willful misunderstanding of the benefits that transplantation may bring with it Plaintive and despondent voices tell us that the effort expended upon these heroic surgical procedures is out of all proportion to the number that can benefit from it, that we are squandering our material and intellectual resources on these adventures at a time when 99 per cent of the world s population cries out for elementary medical care that the number of patients who have carried grafts of kidneys for more than a few months is smaller than the number of people engaged in the research on transplantation

This is an unjust criticism All great advances in medicine must nowadays start with a great capital investment of time and manpower and energy There was a time when the same criticism could have been leveled against research on antibiotics I was working in Oxford when research on penicillin in Professor Florey s entire laboratory was brought to focus in the treatment of just one small boy The point is that the heroic adventures of today are part of tomorrow s ordinary medical care If we thwart or discourage research on transplantation today we are deliberately willing away part of the medical heritage of the future *

Human cardiac transplantation is no longer a technical surgical problem A surgeon should not be permitted to perform this operation simply because he can and wants to do it Should this be permitted the operation would qualify for Shaw s definition of "murderous absurdity[69] and Forsmann s initial evaluation would not be too far from the truth

At present human cardiac transplantation should remain in the province of the small number of groups with a profound commitment and with financial support

*Medawar Sir Peter Medawar s views on transplantation Br Med J 1:373 1968 Quoted with permission

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Clinical communications

Electrocardiogram and vectorcardiogram in ventricular inversion (corrected transposition)

*Benjamin E. Victorica, M.D.**
*B. Lynn Miller, M.D.***
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Gainesville, Fla.

Inversion of the ventricles with transposition of the great arteries (congenital corrected transposition of the great arteries) is a well defined cardiac malformation in which there is a reversal of the left-right relationship of the ventricles with anatomic transposition of the aorta and pulmonary artery.[1,2] The posterior pulmonary artery receives systemic venous blood from a morphologic left ventricle which functions as the "venous ventricle," while the anterior aorta receives pulmonary venous blood from a morphologic right ventricle that serves as the "arterial ventricle." Thus the circulatory pathway is *physiologically "correct."* However, this entity rarely occurs without associated cardiac malformations. Ventricular septal defects, pulmonic stenosis, or an Ebstein-like anomaly involving the atrioventricular valve of the morphologic right ventricle are commonly present.[2-4]

Several investigators[3,5,16] have described the electrocardiographic (ECG) and vectorcardiographic (VCG) features of corrected transposition, but few cases have been correlated with the hemodynamic data. Furthermore, some authors have included varieties of single ventricle with inversion in the analysis.[17] The purpose of this report is to present the ECG-VCG patterns observed with different hemodynamic states in a series of patients with ventricular inversion and two functioning ventricles. All had associated intracardiac malformations of varying severity. We have found that the ECG and VCG are reliable indicators of ventricular overloading just as they are in similar defects in the non-inverted heart.

Materials and methods

We have reviewed nine children with ventricular inversion who were evaluated at the University of Florida Teaching Hospital and met our strict diagnostic criteria. Only patients with apex on the left were included in the series. In all cases the diagnosis of ventricular inversion with two functioning ventricles was based on cardiac catheterization and selective ventricular

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Table I. Clinical findings—Ventricular inversion with two functioning ventricles

	Case no.	Age at catheterization	Sex	Symptoms, signs	Age murmur discovered	Method of diagnosis	Associated defects	Surgery
Group I								
	1	3-6/12 years 8-7/12 years	F*	None None	At birth	C-A	Subvalvar pulmonic stenosis	None
	2	4-2/12 years	M	None	8 weeks	C-A	Ventricular septal defect, pulmonic valvar stenosis, left A-V valve incompetence	None
	3	13-6/12 years	M	None	11 years	C-A	Pulmonic valvar stenosis	None
Group II								
	4	3 months	M	Jaundice Congestive heart failure	At birth	C-A-N	Atrial septal defect, azygos continuation of the inferior vena cava, biliary atresia	None
	5	1 year	F	None	11 months	C-A	Ventricular septal defect, pulmonic valvar stenosis	None
	6	1-6/12 years	F	Cyanosis	At birth	C-A	Ventricular septal defect, pulmonic valvar stenosis, right aortic arch	None
Group III								
	7	6 weeks	M	Congestive heart failure	3 weeks	C-A-S	Ventricular septal defect	Pulmonary artery banding
	8	3 years	F	None	2 years	C-A	Ventricular septal defect, pulmonic stenosis	None
	9	13-8/12 years	M	Chronic congestive heart failure	10 days	C-A-S	Ventricular septal defects (membranous & muscular), coarctation pulmonary arteries, pulmonic valve incompetence	Closure—ventricular septal defect

Abbreviations: F = female; N = necropsy; M = male; S = surgery; C-A = catheterization and angiocardiography; A-V = atrioventricular.

angiocardiography with clear demonstration of the internal anatomic characteristics of the ventricles. Diagnosis on position of the great arteries alone is not acceptable to us. All patients had situs solitus, thus by definition excluding all patients with either proved or suspected asplenia or polysplenia syndromes. Basic clinical information and description of the associated defects is given in Table I.

The ECG-VCG tracings used for analysis were those obtained at the time of admission for cardiac catheterization. Electrocardiograms were recorded on direct writing units and included the classical six standard and augmented limb leads and the eight precordial leads (V_3R to V_7). Tracings were analyzed for rhythm, mean axes, and QRS-T contour. Vectorcardiograms were obtained with a Sanborn Viso-scope Model 569 A using the Grishman cube system. Photographs of the oscilloscopic patterns were made on a Hewlett-Packard 196 A camera in the frontal (F), right sagittal (S), and horizontal (H) planes. The electron beam was interrupted every 2.5 msec. with the blunt end of the dots indicating the direction of inscription. The QRS loops were analyzed for the direction of inscription and the orientation of initial and terminal 0.01 second instantaneous and maximal QRS forces.

Classification. Catheterization data presented in Table II provide a hemodynamic basis for dividing the series into three groups.

Group I consists of three patients with mild pulmonic stenosis in whom the systolic pressure in the venous ventricle was 50 per cent of systemic or less. Case No. 2 al o

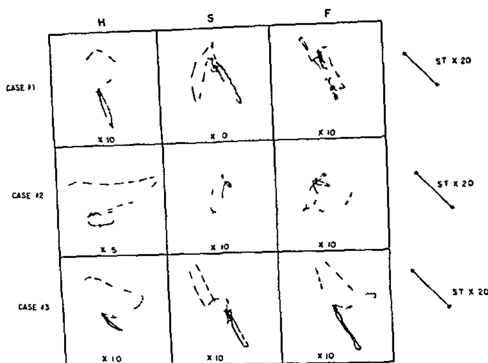


Fig 1 Grishman cube vectorcardiograms of all three cases in Group I Note the completely posterior counter clockwise horizontal QRS loop in each case Key ST = 1 4 mv X = standard and degree of attenuation arrows = direction of inscription H = horizontal S = right sagittal F = frontal

had a small ventricular septal defect with a pulmonary to systemic flow ratio (Qp Qs) of 1 2 1 and moderate left atrioventricular valve incompetence Case No 1 is considered only in Group I although as noted in Table II and in the discussion below this patient progressed to meet the criteria for Group II at the time of a second catheterization

Group II consists of three patients in whom the major hemodynamic effect was either volume or pressure overload of the venous ventricle Case No 4 had an atrial septal defect with a pulmonary to systemic flow ratio of 4 5 1 Cases No 5 and 6 had ventricular septal defects associated with significant pulmonic valvar stenosis resulting in systemic pressures in the venous ventricle and net right to left shunts (Qp/Qs 0 93 1 and 0 6 1 respectively)

Group III consists of three patients with biventricular overload due to the presence of large ventricular septal defects All had venous ventricular peak systolic pressure near systemic levels with left to right shunts ranging from 2 1 1 to 2 8 1 In

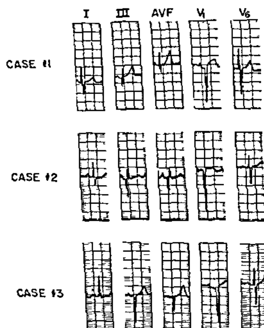


Fig 2 Selected ECG leads from the three cases in Group I Note the QS patterns in V1 representing the posterior displacement of the QRS force in each case and the consistent q wave in Lead III and aVF

Table II. Catheterization data—Ventricular inversion with two functioning ventricles

Case no.	Pressures (mm. Hg)				
	VV*	PA	AV	Ao	VV/AV a
Group I					
1	50/2-5	17/8 (9)§	100/0-5		0.50
2	59/0-3	31/12	98/4-5	98/58 (80)	0.40
3	48/0-6	30/10 (19)	108/2-12	108/70 (90)	0.44
Group II					
4	58/11-19		110/18-32	115/35	0.53
5	84/0-4		85/0-5	87/48 (58)	0.99
6	90/2-8		90/2-10	90/45 (68)	1.0
1†	65 (90)‡/3-6	15/8 (13)	88/3-7	88/60	0.74
Group III					
7	80/0-5	83/32 (45)		98/50 (68)	0.82
8	90/5-10	27/15		116/58 (70)	0.78
9	87/8-14	85/36	107/7-20	104/70	0.81

Abbreviations: VV = venous ventricle; PA = pulmonary artery; AV = arterial ventricle; Ao = aorta; VV/AV or Ao = peak systolic ra[illegible]
† = second catheterization.
‡ = after angiocardiography.
§Parentheses denote mean pressures.
NOTE: Pulmonary blood flow in Cases No. 5 and 6 was estimated assuming a pulmonary venous saturation at 97 per cent. Indicator d[illegible]

addition, Case No. 8 demonstrated pulmonic valvar stenosis and Case No. 9 was found to have bilateral coarctations of the pulmonary arteries and pulmonic valve incompetence.

Results

Pertinent electrocardiographic and vectorcardiographic information is given in Tables III and IV.

Group I (Cases No. 1 to 3). The initial (0.01 sec.) QRS vector is oriented directly leftward or leftward, posteriorly, and superiorly (Fig. 1). The QRS loop is completely posterior in all, predominantly inferior in two and superior in one. The terminal QRS forces are directed rightward and posteriorly in all, superiorly in two and inferiorly in one. The QRS loops in the H plane are very similar *in* the three cases, being open loops with counterclockwise (CCW) inscription. Frontal plane QRS inscription ranges from predominantly CCW in one to purely clockwise (CW) in another.

The electrocardiograms (Fig. 2) demonstrate a mean QRS axis in the frontal plane of +25 degrees in two cases and -50 degrees in one. Initial q waves present in Leads III and aV_F in all three are deeper in Lead III in each instance. The QRS morphology in the precordial leads is uniform in all cases, reflecting the posterior displacement of the forces. A consistent QS pattern is present in V_1, while in V_6 there are no initial q waves but rather RS complexes.

Group II (Cases No. 4 to 6). Vectorcardiograms (Fig. 3) reveal initial QRS forces directed leftward and superiorly in every case. In two the 0.01 sec. vector is posterior and in one directly leftward at 0

	Oxygen saturation (%)						Qp/Qs	Selective angiocardiography
SVC	RA	VV	PA	AV	Ao			
68			67	98			1 1	None
	64		70	98			1 2 1	Venous ventricle arterial ventricle
82			81		97		1 1	Venous ventricle
61		90			98		4 5 1	Venous ventricle arterial ventricle
	54	57			91		0 93 1	Venous ventricle
61	62	62			83		0 6 1	Venous ventricle
			74		98		1 1	Venous ventricle
72			84		95		2 1	Venous ventricle left atrium
58			78		93		2 3 1	Venous ventricle
	80		91		97		2 8 1	Arterial ventricle pulmonary artery

SVC = pe e ca RA = ght t m Qp = p lm nary blood flow Qs = s t mic blood flow

ethod howed ght to-left h t Case No 8

degrees The QRS loops curiously have a similar configuration in the H and F planes with predominantly CW inscription and the major portion of the loop directed rightward anteriorly and inferiorly in every case The terminal QRS forces are uniformly rightward anterior and inferior

The mean frontal QRS axis on the ECG (Fig 4) is +130 degrees in all three cases and all have q waves in Leads III and aV_F Unlike Group I a qR pattern in the right precordial leads is the rule There are no initial q waves in V_6 all demonstrating RS complexes These ECG VCG findings are considered to be indicative of hypertrophy of the venous ventricle

Group III (Cases No 7 to 9) In the VCG (Fig 5) the initial (0 01 sec) QRS forces are all leftward two being superior and one inferior In contrast with the two previous groups the initial QRS forces are anteriorly directed in every case In Case No 7 following the initial QRS vector the H plane QRS loop continues leftward but then the loop reverses and the major portion is rightward and anterior with a CW inscription The vectorcardiograms in Cases No 8 and 9 show a different pattern with large anterior and posterior QRS forces and CCW inscription in the H plane The F plane in Case No 8 shows CCW inscription of the QRS while Cases No 7 and 9 are CW

In the electrocardiograms (Fig 6) the mean QRS axis in the F plane ranges between +50 degrees and +100 degrees An initial q wave is present in Lead III in all but no q waves are present in the precordial leads Leads V_1 and V_6 show RS complexes of varying magnitude but Lead V_1 in Case No 7 demonstrates an rSR pattern Large biphasic mid precordial QRS complexes

Table II Catheterization data—Ventricular inversion with two functioning ventricles

Case no	Pressures (mm Hg)				
	VV*	PA	AV	Ao	VV/AV or Ao
Group I					
1	50/2 5	17/8 (9)§	100/0-5		0 50
2	39/0 3	31/12	98/4 5	98/58 (80)	0 40
3	48/0-6	30/10 (19)	108/2 12	108/[illegible]0 (90)	0 44
Group II					
4	58/11 19		110/18 32	115/35	0 53
5	84/0-4		85/0-5	82/48 (58)	0 99
6	90/2 8		90/2 10	90/45 (68)	1 0
1 †	65 (90)‡/3 6	15/8 (13)	88/3 7	88/60	0 [illegible]4
Group III					
7	80/0-5	83/3[illegible] (45)		98/50 (68)	0 8[illegible]
8	90/5 10	27/15		116/58 (70)	0 [illegible]8
9	87/8 14	85/36	107/7 20	104/70	0 81

*Abbreviations VV = venous ventricle PA = pulmonary artery AV = arterial ventricle Ao = aorta VV/AV or Ao = peak systolic ra

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Group II (Cases No 4 to 6) Vectorcardiograms (Fig 3) reveal initial QRS forces directed leftward and superiorly in every case In two the 0 01 sec vector is posterior and in one directly leftward at 0

Vo me 86
N mb 6

Table IV Vectorcardiographic findings—Ventricular inversion with two functioning ventricles

	Horizontal plane○					Right sagittal plane	Frontal plane				
	QRS loop				T loop	QRS loop	QRS loop			T loop	
Case no	Init (0.01 sec)	Max	Term (0.01 sec)	Insc	Max	Insc	Init (0.01 sec)	Max	Term (0.01 sec)	Insc	Max
Group I											
1	+35	+90	+130	CCW	− 0	CW	−40	+50	−140	CW	+10
	+15	+30	+150	CCW	−30	CCW	−40	+120	+150	CW	+15
3	0	+ 5	+1[illegible]5	CCW	−45	CW	−10	−110	−120	CCW	+60
Group II											
4	+20	−160	−150	CW		CCW	−45	+160	+160	CW	+80
5	−10	−150	−130	CW (∞)	−10	∞ (CCW)	−10	+165	+160*	∞ (CW)	+5
6	−5	−120	−130	CW		CCW	−10	+60	+150	CW	+50
1†	+35	−150*	−150	CW	−40	CCW	−60	+45	+160*	CW	+ 0
Group III											
7	−60	−1 0	−120	CW		CCW	−40	+100	+130	CW	+60
8	−65	+65	+80	CCW	−80	CW	+30*	+40	+35	CCW	+90
9	−65	+120	−140	CCW	−60	∞ (CW)	−30	+120	+145	CW	+60

Abb t CW = lockwise CCW = cou t lockwise ∞ = comple ○ = In the horizo tal plane a t rio is cons de ed as neg ti I it Max T m = t al max mal nd te m nal QRS f ce I sc = d ection of nscript on of the QRS loop
† = at seco d th t t

are present in all three cases These ECG VCG findings are felt to represent biventricular hypertrophy

Discussion

Leftward and superior orientation of the initial QRS forces in inversion of the ventricles is a consistent and well-documented phenomenon (Fig 7) This reversal of septal depolarization is attributed to inversion of the conduction pathways (atrioventricular node His bundle and bundle branches) clearly shown by the work of Lev Licata and May [19] The resultant ECG manifestations are the presence of qR patterns in Leads III and aV_F and reversal of the precordial q wave pattern as first described by Anderson and co workers [5] Little emphasis however has been placed on the study of the orientation and configuration of the rest of the QRS forces particularly as they relate to the presence or absence of associated cardiac malformations and their hemodynamic consequences (ventricular overload) By limiting our analysis to unequivocal cases of ventricular inversion with situs solitus cardiac apex on the left and two functioning ventricles we have confirmed the presence of consistent ECG VCG patterns

In cases of inversion with minor associated anomalies resulting in low venous ventricular pressure (our Group I) the ECC VCG shows a pattern which may be considered normal for this cardiac condition [7,12,14] In these patients the VCG shows maximal and terminal QRS forces oriented posteriorly and the QRS loops in the H plane are open and wide with CCW inscription The few published vector cardiograms whether recorded by the Frank[20] or Grishman[21] system show similar configurations [1,16] The ECG pattern of QS complexes in the right precordial leads (V_4R to V_1) seen in our patients has been described in isolated cases in the literature [8,10,12] Occasional cases with small r deep S in Lead V_1 have been seen [7,14]

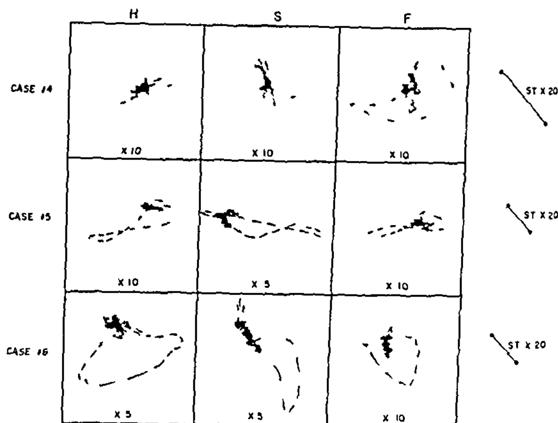


Fig. 3. Cube vectorcardiograms in all three cases of Group II. Note that while the initial QRS forces are oriented leftward either at 0 degrees or more posteriorly, the major QRS forces are anterior and rightward in each case. Key same as Fig. 1.

Table III. Electrocardiographic findings—Ventricular inversion with two functioning ventricles

	Case no.	Rhythm	P	Mean axis (degrees) QRS	Mean axis (degrees) T	P R (sec) II	Q/R/S Pattern (mm) III	Q/R/S Pattern (mm) aVF	Q/R/S Pattern (mm) V₁	Q/R/S Pattern (mm) V₆	T Waves V₁	T Waves V₆
Group I												
	1	*NSR	+60	+25	+[illegible]0	0 12	5/5/[illegible]	[illegible]/[illegible]/4	19/0/1[illegible]	0/11/13	+	+
	2	Variable 2 AV Block	+65	+[illegible]5	+40	0 16	10/6/0	6/6/0	[illegible]/0/0	0/[illegible]/3	+−	+
	3	NSR 1 AV Block	+60	−[illegible]0	+ 0	0 0	1[illegible]/0/7	6/0/[illegible]	1[illegible]/0/[illegible]0	0/10/10	+	+
Group II												
	4	2 AV Block	+80	+130	−50	0 11	13/18/0	7/1[illegible]/0	3/5/0	0/7/16	+	−+
	5	Wandering pacemaker	—	+130	+[illegible]0	0 10-0 12	4/11/0	[illegible]/8/0	[illegible]/[illegible]1/1	0/6/10	+	+
	6	NSR	+60	+130	+60	0 11	7/13/0	5/15/0	4/13/0	0/8/10	−+	+
	1†	NSR	+60	+70	+80	0 12	5/11/1	[illegible]/9/3	1[illegible]/16/[illegible]	0/1[illegible]/15	−+	+
Group III												
	7	NSR	+60	+110	+60	0 10	[illegible]/17/0	6/28/1	0/1/1/6	0/15/14	−+	+−
	8	NSR	+[illegible]0	+[illegible]0	+90	0 13	2/7/0	0/8/0	0/10/4[illegible]	0/1[illegible]/3	+	+−
	9‡	NSR 1 AV Block	+100	+60	+110	0 6	4/3/5/9	3/8/0	0/1[illegible]/5	0/1[illegible]/19	+	−+

*Abbreviations: AV = atrioventricular; NSR = normal sinus rhythm.
† = second catheterization.
‡ = complete AV block after surgery.

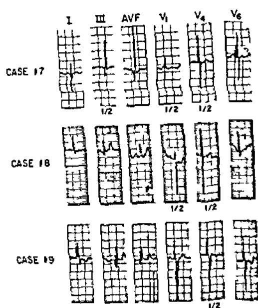


Fig 6 Selected ECG leads in all three cases of Group III Note the absence of q waves both in the right and left precordial lead presence of a q in Lead III and large biphasic QRS complexes in V4 1/2 standardization 1 0 mv = 5 mm

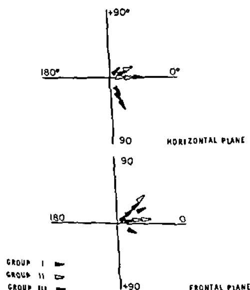


Fig 7 Composite of the initial (0 01 sec) QRS vector in the horizontal and frontal planes for all 9 case of inver ion of the ventr cles w th two funct io i g ventricles In the hori ontal plane the anterio quadra t are co idered negati e while the po terior are po ti e

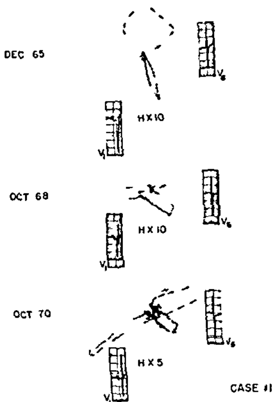


Fig 8 Serial H plane vectorcardiograms in Case No 1 howing progression from loops characteristic of Group I *(Dec 65)* to Group II *(Oct 70)* Note that the QRS pattern in V1 changes from a QS to a qR

from that observed in double inlet left ventricle and inversion[22] Furthermore a qR pattern in V_1 may be present in some cases of severe right ventricular hypertrophy in a heart with non inversion of the ventricles In such cases the initial forces in the frontal plane will generally help distinguish between the two

Those cases with hemodynamic evidence of overload of both ventricles (our Group III) demonstrate ECG VCG patterns consistent with biventricular hypertrophy In striking contrast with the two previous groups the initial 0 01 sec QRS forces while leftward are distinctly anterior This finding could not be explained by the orientation of the ventricular septum as determined by angiocardiography The ECG representation of anterior displacement of the initial QRS forces is absence of q waves in both right and left precordial leads In Case No 7 the leftward and CCW early

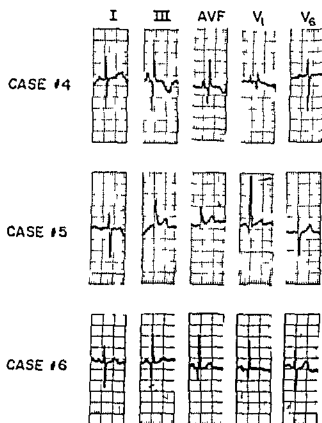


Fig 4 Selected ECG leads in all three cases of Group II Note the right axis deviation significant initial q waves in Leads III and aVF and constant qR pattern in V_1

In those cases with either volume or pressure overload of the venous ventricle (our Group II), the maximal and terminal QRS forces, in contrast with the previous group, have a rightward and anterior orientation as a result of the hypertrophy of the right sided morphologic left ventricle The VCG in all three patients shows CW inscription of the QRS loop in the H plane Ruttenberg and associates[2] have published a VCG which shows the same general configuration of the QRS from a child with similar hemodynamic findings

The constant ECG feature observed in Group II is the well recognized qR pattern in V_1 generally described as a common finding in corrected transposition This pattern was present in 60 per cent of the cases analyzed by Schiebler and associates[3] However tall R waves in V_1 and predominant S waves in V_6 are signs of hypertrophy of the right sided ventricle On review of the literature of corrected transposition with associated venous ventricle hypertension we found similar patterns[5 6 10 2]

Present evidence suggests that the ECG VCG of corrected transposition with venous ventricular overload is indistinguishable

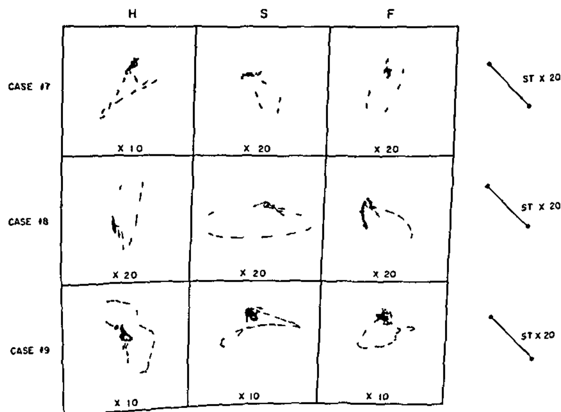


Fig 5 Cube vectorcardiograms in all three cases of Group III Note that the initial QRS forces while leftward are anterior in all Cases No 8 and 9 show large anterior and posterior QRS forces Key same as Fig 1

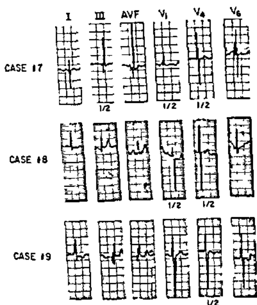


Fig 6 Selected ECG leads in all three cases of Group III Note the absence of q waves both in the right and left precordial lead presence of a q in Lead III and large biphasic QRS complexes in V_4. ½ standardization 1 0 mv = 5 mm

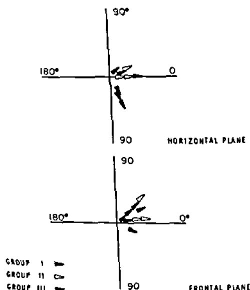


Fig 7 Composite of the initial (0 01 sec) QRS vector in the horizontal and frontal planes for all 9 cases of inversion of the ventricles with two functioning ventricles In the horizontal plane the anterior quadrants are considered negative while the posterior are positive

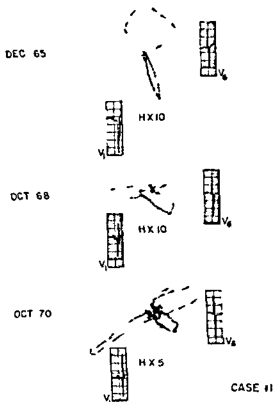


Fig 8 Serial H plane vectorcardiograms in Case No 1 showing progression from loops characteristic of Group I *(Dec 65)* to Group II *(Oct 70)* Note that the QRS pattern in V_1 changes from a QS to a qR

from that observed in double inlet left ventricle and inversion[23] Furthermore a qR pattern in V_1 may be present in some cases of severe right ventricular hypertrophy in a heart with non inversion of the ventricles In such cases the initial forces in the frontal plane will generally help distinguish between the two

Those cases with hemodynamic evidence of overload of both ventricles (our Group III) demonstrate ECG VCG patterns consistent with biventricular hypertrophy In striking contrast with the two previous groups the initial 0 01 sec QRS forces while leftward are distinctly anterior This finding could not be explained by the orientation of the ventricular septum as determined by angiocardiography The ECG representation of anterior displacement of the initial QRS forces is absence of q waves in both right and left precordial leads In Case No 7 the leftward and CCW early

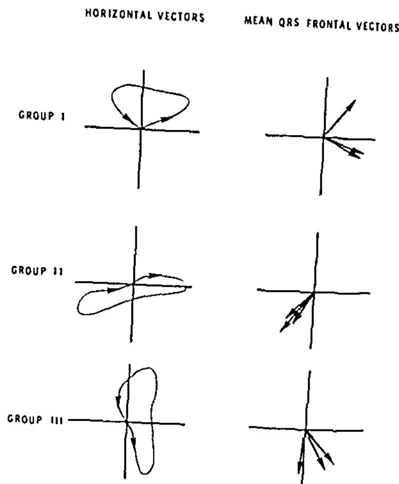


Fig. 9. Derived Grishman system horizontal plane QRS loops and observed mean frontal QRS vectors in ven tricular inversion with two *functioning ventricles* (corrected transposition). *Group I*, minor associated defects; *Group II*, venous ventricular overload; *Group III*, biventricular overload.

QRS forces are followed by reversal of inscription to a larger rightward and anterior portion of the QRS loop. This represents biventricular hypertrophy, right greater than left in a patient who is only six weeks old. The horizontal QRS loops of cases No. 8 and 9 have a similar open and CCW inscription with large anterior and posterior forces which is not unlike a case shown by Ruttenberg and co-workers.[22]

The ECG criteria for biventricular hypertrophy are large biphasic RS complexes in the mid precordial leads. Such prominent voltages are not present in any of the six cases in Groups I and II.

Case No. 1 presents a narrative further substantiating the impression that the ECG-VCG described in the different groups illustrates varying physiologic states. Serial tracings in this patient (Fig. 8) show an evolution of the characteristics associated with Group I to Group II as the venous ventricular pressure increased due to progressive pulmonic stenosis.

Derived H plane QRS loops and plotted mean F plane QRS vectors (Fig. 9) demonstrate the features which best distinguish ventricular overload states in corrected transposition. In cases with minor associated anomalies, the QRS loop is posterior with CCW inscription and there is borderline or frank left axis deviation. With venous ventricular overload the QRS loop is predominantly anterior with CW inscription and there is right axis deviation. Biventricular overload deviates the initial QRS forces anteriorly; the QRS loop may be leftward and CCW as shown or more rightward and anterior if the venous ventricle overload is predominant. The mean frontal QRS vector may be in normal range.

Summary

The vectorcardiographic (VCG) and electrocardiographic (ECG) features in nine cases of ventricular inversion with two functioning ventricles (congenital corrected transposition of the gr[illegible]arteries) and

associated cardiac malformations were correlated with their hemodynamic states All three cases with low venous ventricular pressure showed a similar VCG pattern with a posterior and completely counterclockwise horizontal QRS loop The ECG showed a leftward QRS axis QS complexes in V_1 and RS complexes in V_6 These findings are normal for ventricular inversion without major associated defects Three patients with isolated pressure or volume overload of the venous ventricle showed large leftward and posterior initial QRS forces followed by a predominantly clockwise and rightward horizontal QRS loop The ECG showed right axis deviation qR complexes in V_1 and rS complexes in V_6 These findings are considered to represent venous ventricular hypertrophy Three patients with hemodynamic situations which would be expected to result in biventricular overload demonstrated varying degrees of anterior displacement of the horizontal QRS loop two with counterclockwise inscription and one predominantly clockwise The initial QRS forces although leftward and superior as in the other groups were anterior in each case The ECG demonstrated normal or rightward QRS axis no precordial q waves and large biphasic RS complexe in the mid precordial leads These findings are considered to represent biventricular hypertrophy One patient had serial tracings which revealed progressive ECG VCG changes due to increasing venous ventricular hypertension secondary to increasing pulmonic stenosis

These findings indicate that the ECG VCG accurately reflect the anatomy and hemodynamics in ventricular inversion

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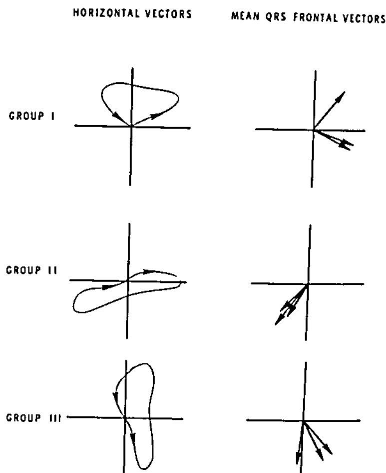


Fig 9 Derived Grishman system horizontal plane QRS loops and observed mean frontal QRS vectors in ventricular inversion with two functioning ventricles (corrected transposition) *Group I* minor associated defect *Group II* venous ventricular overload *Group III* biventricular overload

QRS forces are followed by reversal of inscription to a larger rightward and anterior portion of the QRS loop This represents biventricular hypertrophy right greater than left in a patient who is only six weeks old The horizontal QRS loops of cases No 8 and 9 have a similar open and CCW inscription with large anterior and posterior forces which is not unlike a case shown by Ruttenberg and co workers [22]

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Summary

The vectorcardiographic (VCG) and electrocardiographic (ECG) features in nine cases of ventricular inversion with two functioning ventricles (congenital corrected transposition of the teries) a

Level of the base of the mitral valve

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Mean left atrial pressure is a significant quantity in the assessment of left ventricular filling pressure and pulmonary venous pressure These quantities in turn provide information concerning left ventricular performance and the development of pulmonary edema which are of real concern in the management of postoperative patients for heart and lung surgery A number of guidelines have been presented in the literature for the determination of the zero pressure level for systemic veins for the patient supine [1-4] However the use of these guidelines for the left atrium and for patients in positions other than supine is in principle incorrect Especially now that flow guided balloon catheters enable us to monitor pulmonary capillary wedge pressure in the Intensive Care Units a new investigation seems justified

In addition continuous monitoring of left atrial pressure after heart or lung surgery has shown significant changes in this parameter when patients were turned or tilted This too might have been due to conventional methods for zero pressure levelling Hence in order to determine whether these pressure changes were due to conventional methods for zero pressure determination the vertical distance from the base of the mitral valve to a marker placed at mid sternum was determined radiologically Furthermore we have investigated how well these distances correlated with thorax dimensions patient height and weight

Ten patients were chosen for this study and all were at least one month postoperative for replacement of the mitral valve (Starr Edwards ball valve) These patients were chosen since the mitral valve presented a clear unambiguous image on the x ray film and did not require any invasive procedures Since a simple reference point was desirable all distances were measured with respect to the center of the sternum The choice of the base of the mitral valve rather than some other point in the left atrium or left ventricle was dictated primarily by the patients available for this study That is the base of the mitral valve represented the only clear unambiguous image on the x ray films to which distances could be easily measured It can be argued however that this is not necessarily the most desirable point of reference with mid ventricle or mid atrium possibly a better choice

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Table II Physical data on patients

Patient no	Age (years)	Sex	Height (cm)	Weight (Kg)	Surface area (M^2)	Sternum length (cm)	Thorax width (cm)	Thorax depth (cm)
1	17	F	156	47 4	1 45	16	22	19
2	42	F	169	52 3	1 60	18	27	21
3	56	F	158	59 3	1 60	25	24 5	22
4	49	F	157	60	1 61	14 5	22	22 5
5	33	F	167	50	1 52	16	24	20
6	37	M	174	73 5	1 88	21	30	24
7	48	M	163	55 5	1 60	19	27	0
8	64	M	177	65	1 93	25	32	7
9	40	F	156	40 2	1 35	17	23 7	18
10	43	F	168	50 5	1 57	17 5	26 5	21

photo measurements the physiological distances for the projection used and (3) for each patient position use information from steps 1 and 2 from all camera positions to determine the three coordinates of the mitral valve with respect to the patient coordinate system

Since all the patients had Starr Edwards ball valves some simplification in the methodology was possible The diameter of the ball in the valve for each photo was used to determine the scale factor This meant that only one calibrated photo need be taken to initially determine the actual ball diameter For all subsequent pictures this diameter defined the scale factor without any reference to source patient image distances

Results

With the mid sternum marker as the reference point the data in Table I represent the location of the base of the mitral valve for all 10 patients in the 6 indicated positions Within each box there are 4 numbers The first three to the left in each box represent the x y and −z coordinates of the mitral valve with respect to the mid sternum marker x represents the direction from the mid sternum marker to the feet y the distance from the marker to the left arm and −z the distance into the thorax The number to the right in each box (expressed as a percentage) is the standard error of the estimate with respect to the distance between the marker and mitral valve

The data in Table II show the height weight body surface area sternum length thorax width and depth at mid sternum level for the 10 patients listed in the same order as Table I

For each patient position the vertical distance of the base of the mitral valve below the marker (Ŷ) was calculated and a linear regression analysis was performed for height weight body surface area sternum length thorax width and depth For each of the 6 positions the mean distance below the marker (average for all patients) together with the standard error of the estimate (SEE)

$$SEE = \frac{1}{N} \sum_{i=1}^{N} \left[(Y - \bar{Y})^2\right]^{\frac{1}{2}} \qquad (1)$$

is shown in Table III Next to each entry is the improved standard error of the estimate resulting from the linear regression analysis

Discussion

For the patient in supine position a comparison between our results and those of previous studies can be made For example Lyons and colleagues[1] placed their patients in a supine position on a rigid surface and chose the zero level as 10 cm above that surface Richards and associates[2] and Cournand and co workers[3] placed the level as 5 0 cm and 6 6 cm respectively below the Angle of Louis (angle between the manubrium and the anterior surface of the sternum) Weil and associates[4] and Burri

*Table I Location of the base of the mitral valve**

Patient no	Coordinates†	On right side 90 (cm)	On right back 45 (cm)	Flat on back (cm)	On left back 45 (cm)	On left side 90 (cm)	Tilted 30° head up (cm)
1	x	6 5	7 3	3 6	4 8	4 3	4 0
	y	4 9 8 4%‡	5 4 0 8%	3 3 6 0%	2 7 2 4%	4 1 6 2%	2 8 3 4%
	−z	5 3	4 5	7 7	7 0	7 0	7 6
2	x	6 5	6 7	4 3	6 1	5 7	7 3
	y	−1 1 5 2%	1 5 5 0%	2 3 7 5%	2 7 1 8%	2 7 12%	1 4 7 8%
	−z	6 9	6 6	8 2	6 1	5 7	7 3
3	x	5 9	6 9	6 2	7 1	6 4	6 4
	y	0 7 9 1%	4 3 1 1%	3 8 4 4%	3 7 4 1%	3 0 6 7%	4 2 5 5%
	−z	8 3	6 5	5 6	7 1	6 7	5 9
4	x	6 4	4 8	4 5	5 7	4 3	1 7
	y	2 4 2 9%	4 1 1 0%	4 3 4 9%	1 8 2 8%	4 8 6 0%	3 4 1 5%
	−z	7 0	8 2	7 9	6 7	7 6	8 8
5	x	4 7	5 2	3 7	4 6	3 4	4 3
	y	2 7 4 3%	6 5 6 1%	1 4 5 9%	−0 3 1 6%	−0 8 5 8%	2 0 3 9%
	−z	7 4	4 3	7 6	6 6	7 7	6 7
6	x	3 9	3 4	3 4	3 7	3 6	4 8
	y	1 0 3 1%	2 0 6 1%	1 6 7 6%	6 0 2 7%	2 3 5 9%	4 2 3 7%
	−z	8 5	9 3	9 0	8 8	9 0	8 0
7	x	4 8	5 8	2 8	4 2	3 2	4 4
	y	1 0 0 1%	3 6 2 4%	3 4 7 3%	3 6 3 4%	3 7 13%	3 4 6 ?%
	−z	8 0	7 0	8 8	8 0	7 4	9 1
8	x	4 1	4 1	3 6	5 5	4 2	4 3
	y	5 0 0 7%	3 8 0 6%	4 6 4 7%	5 2 6 4%	4 4 8 0%	3 7 5 6%
	−z	10 8	9 2	9 4	8 5	10 0	9 5
9	x	5 0	3 7	3 8	3 9	3 0	2 0
	y	0 6 5 9%	1 6 3 0%	2 2 1 1%	3 5 8 3%	3 2 8 4%	2 7 4 1%
	−z	5 9	6 3	6 1	6 6	6 4	7 0
10	x	6 7	5 7	4 6	4 6	3 5	5 8
	y	3 8 2 0%	1 9 5 5%	2 6 0 7%	2 0 2 6%	2 8 2 3%	1 9 10%
	−z	6 2	7 2	7 5	7 4	7 6	7 3

*Measured with respect to the marker placed at mid sternum
†The +x axis points toward the feet the +y axis toward the left arm the −z axis into the thorax
‡Represents standard error of the estimate (SEE) with respect to total distance from the marker to the base of the mitral valve

Clinical and analytic methods

While the analysis which forms the basis for the clinical methods is somewhat involved the basic concepts are not difficult By way of outline these basic considerations are summarized below A more detailed description is in the **Appendix**

In order to most simply determine the vertical distance of the mitral valve below the marker (necessary to define a reference point and located at mid sternum) a single calibrated x ray in a horizontal projection is all that is required A single photo necessarily "sees" only a two dimensional projection and therefore one coordinate is lost As all three coordinates are desired the missing coordinate is recovered by repositioning the camera

In practice the situation is not so ideal Due to the limited viewing field of the x ray camera quite often a simple horizontal projection does not include the image of both the valve and the marker This requires viewing angles which do not allow simple inspection of the photos to reveal physiological distances with respect to a convenient patient coordinate system In addition the distance between the x ray source and patient and between the patient and camera varies as the camera was repositioned thereby changing the scale factor of every photo

Hence an analysis of the geometry is required That is (1) determine the camera position with respect to the patient coordinate system (2) determine from actual

possibly to an extent not related to the quantities used here for the regression analysis

Height results in the greatest reduction in SEE in RS — 45 degrees frontal and tilt but in the remaining three positions it is last or next to last Likewise thorax width results in the greatest improvement in the RS — 90 degrees LS — 45 degrees LS — 90 degrees positions but is last or next to last in the remaining three Weight in every case except one (LS — 90 degrees) is third place with respect to reduction in SEE Surface area and thorax depth vary between second and fourth place Sternum length is last or next to last in every position except one and clearly emerges as the one parameter least likely to correlate with mitral valve location

It is the opinion of the author that this degree of improvement in the SEE does not justify the use of a linear regression equation to estimate the base of the mitral valve for adults in the range of height weight etc covered in this study However the use of the mean values indicated in Table III is justified as a guideline for the positioning of the zero level in adults in the positions indicated

While no data are presented for the patient sitting upright some estimate can be made For the patient supine (flat on back) the x coordinate (distance from marker to BMV in the direction of the feet) averages 4 0 cm Tilted at 30 degrees this distance increases to 4 5 cm As it appears that the heart is well tethered within the thoracic cavity we do not expect this distance to increase appreciably as the patient sits fully upright therefore we estimate in the fully upright position the BMV is 5 cm below the central sternum marker

As stated above the main purpose of this investigation was to find more exactly the zero level for left heart pressures A stimulus for this work was the finding in our intensive care units that continuous monitoring of left atrial pressure (LAP) after open heart surgery showed remarkable changes in this parameter when patients were turned or tilted This happened even after readjusting the transducers according to the rules of Richards and co workers[2] Our studies show that this method is indeed misleading especially when patients were turned on their right side (Table III) Whether the implementation of our guide lines will reduce the described changes in LAP still has to be proved In any event their use will yield more insight into the hemodynamic effects of position Furthermore the use of Swan Ganz balloon catheters has shown the value of pulmonary capillary wedge pressure in establishing the prognosis of patients with myocardial infarctions If this parameter (or end-diastolic pulmonary artery pressure or left atrial pressure directly) is monitored continuously for trend analysis it is necessary to know where to place the transducers in every position of the patient who will be moving much more frequently than after an operation

Summary

The location of the base of the mitral valve was determined in 10 adult patients using a radiologic technique The mean vertical distance below a marker placed at mid sternum was for the patient

on right side	−2 1 cm (− = up)
right side—back 45 degrees	2 4 cm
flat on back	7 8 cm
left side—back 45 degrees	7 3 cm
left side	3 0 cm
tilted head up 30 degrees	8 9 cm

The standard error of the estimate is less than 2 cm in all positions For the patient sitting upright we estimate the distance to the BMV to be 5 0 cm below the mid sternum marker

While some improvement in the patient to patient error could be made through linear regression based on height weight etc the degree of improvement—42 per cent or less reduction in standard error of the estimate—would not justify its use in clinical practice The above guidelines however do provide a useful guide for setting the zero level at the base of the mitral valve

The author thank Mr A den Boer for his assistance in obtaining the data and Miss I de Widt for assistance in the analysis of the data The authors also gratefully acknowledge the voluntary multiple retyping of this manuscript by Mrs Joan Brower

Table III. Vertical distance from marker to base of mitral valve and results of linear regression analysis

	Patient position					
	On right side	*On right back*	*Flat on back*	*On left back*	*On left side*	*Tilted 30°*
Mean vertical distance to mitral valve (cm)	−2.1	2.4	7.8	7.3	3.0	8.9
Uncorrelated SEE	1.9	2.0	1.1	1.7	1.5	1.0
SEE correlated with height	1.9	1.6	8	1.3	1.5	6
% reduction SEE	5%	18%	31%	19%	[illegible]0%	35%
SEE correlated with weight	1.9	1.7	9	1.2	1.4	8
% reduction SEE	1.2%	12%	21%	31%	2.4%	21%
SEE correlated with surface area	1.9	1.7	85	1.2	1.5	7
% reduction SEE	1.2%	15%	29%	30%	1.2%	30%
SEE correlated with sternum length	1.9	1.9	1.1	1.2	1.5	9
% reduction SEE	0%	5.5%	3%	28%	1.1%	8.9%
SEE correlated with thorax width	1.8	1.8	1.0	1.0	1.3	9
% reduction SEE	4.7%	8.9%	7.4%	42%	9.7%	2.7%
SEE correlated with thorax depth	1.9	1.7	1.0	1.0	1.5	9
% reduction SEE	2.1%	16%	8.6%	36%	1.2%	4.1%

and Allgower[5] allow for patient to patient variation by using respectively 1/2 and 3/5 of the thoracic diameter measured from the dorsal surface to the Angle of Louis. Debrunner and Buhler[6] compared the resulting venous pressure for these various techniques for "zero" level determination in 26 patients undergoing right heart catheterization. Except for the method used by Lyons and colleagues,[1] all agreed acceptably well.

Our data in Table III show that the base of the mitral valve (BMV) is 7.8 cm (SEE 1.1 cm) dorsal to the mid sternal marker for the patient in the supine position. When the measurement is made with respect to the dorsal surface the distance is 13.6 cm showing that the method of Lyons and co-workers[1] results in an overestimate of left heart pressures by about 4 cm H_2O which is consistent with the findings of Debrunner and Buhler.[6] Furthermore correlation with respect to thoracic depth results in only a small reduction (8.6 per cent) in standard error (Table III). Therefore those rules which place the zero level as some fraction of thorax depth will be no more accurate in adults than some fixed distance measurement. However, if this is done, our data indicate that the estimate of the BMV is 0.64 times thorax depth measured from the dorsal surface. This is in accordance with the work of Burri and Allgower.[5]

For patients in positions other than supine there appears to be no literature with respect to the position of the BMV and the data shown in Table III represent the first report on this subject.

It was originally thought that a linear regression analysis might substantially reduce the standard error of the estimate. Unfortunately, while linear regression analysis provides some improvement in the standard error of the estimate in every case, the improvement is not especially remarkable. The improvement is greatest in the RS − 45 degrees,* frontal, LS − 45 degrees and tilted positions (about 18 per cent, 31 per cent, 42 per cent, and 35 per cent reduction in SEE), while the SEE in the RS − 90 degrees and LS − 90 degrees positions show virtually no reduction at a[ll] (4.7 per cent and 9.7 per cent). In th[e] RS − 90 degrees and LS − 90 degree[s] positions the thoracic cavity is somewha[t] more deformed than in the other positions—

*Thes[e] abbre[vi]at[i]ons represent the follow[in]g patient po[si]t[i]ons: RS-90, patie[n]t fully on r[i]ght side; RS-45, [pa]rtially on right s[i]de and right back form[i]ng an angle of 45 degrees; F, flat on back; LS-4[5], part[i]ally on left s[i]de and b[ac]k forming an angle of 45 degrees; LS-90, fully o[n] left side.

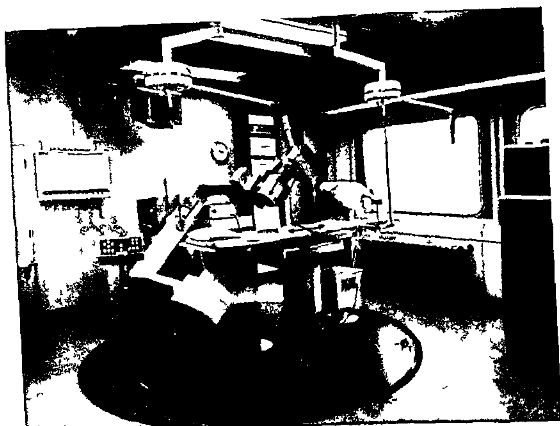


Fig 1 The apparatus used to measure position of the base of the mitral valve is shown The arrows indicate the degrees of freedom available and the C arm angle Φ and table angle Φ are defined The control panel shown on the left side controls all motion except the limited horizontal motion of the table top The x ray photo image i recorded on film and is also stored on a video disk and displayed on the monitor screen

III *Camera position* A marker placed midway on the sternum (shown in Fig 2) forms the center of the coordinate system shown in Fig 3 The +x axis points toward the feet +y to the left arm and +z out of the thorax This convention is maintained regardless of the actual patient position with respect to the x ray table and C arm and is referred to here as the patient co ordinate system The camera position is expressed by the unit vector $\hat{O}$ with respect to the patient coordinate system as shown in Fig 3

As shown in Fig 1 the camera position is originally recorded as the C arm angle ϕ and table angle ϕ_t This information to gether with the patient position (frontal left side 4ɔ degrees etc) is sufficient to define the camera position with respect to the patient coordinate system Mathe matically this is simply a transformation from one coordinate system to another

For a simple rotation about the patient s x axis (longitudinal axis) the camera posi tion is given by equation (3)

$$\hat{O} = -\sin\phi \ \sin\phi_t\, i + (\sin\phi \ \cos\phi_t \cos\gamma + \cos\phi \ \sin\gamma) j + (\cos\phi \ \cos\gamma - \sin\phi \ \cos\phi_t \sin\gamma) k \quad (3)$$

γ represents the patient rotation angle (0 frontal +90 lying on right side −90 on the left side etc) If the patient is tilted (rotation about his y axis) the camera position is given by equation (4)

$$\hat{O} = -(\sin\phi \ \sin\phi_t \cos\gamma + \cos\phi \ \sin\gamma) i + \sin\phi \ \cos\phi_t j \ (\cos\phi \ \cos\gamma - \sin\phi_t \sin\phi_t \sin\gamma) k \quad (4)$$

γ represents the tilt angle (0 for flat on back + 4ɔ if tilted head up at 4ɔ)

IV *Valve location* Equations (3) and (4) presents the camera location (a unit vec tor) with respect to the patient coordinate

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Appendix

I *Apparatus* The system described here consisting of a floating table C arm, and rotating floor was designed in house and is believed to be unique Fig 1 shows the table and C arm image intensifier, control panel and TV monitor The arrows superimposed on the photograph illustrate the degrees of freedom available The camera position is defined by the C arm angle ϕ and table angle ϕ_t as shown in Fig 1

The image intensifier is a 6 inch Philips unit and a 70 mm Philips camera is used for recording the image With the exception of limited horizontal motion (30 cm) of the table top all motion is powered by electric motors and is controlled at the control panel As the photo is taken the image is simultaneously stored on a video disk This picture is instantaneously available to verify that the exposure is correct and that the image is suitable for analysis

There are a number of safety features incorporated whereby power is turned off when parts of the C arm come in contact with the table or patient

II *Patient procedure and scale factor determination* The patient is placed on the table and raised to a height permitting positioning of the C arm A lead marker in the shape of an X is placed midway on the sternum With the C arm in the 90 degrees position (a horizontal projection) the position of the artificial mitral valve is determined and an ink mark is placed on the side of the chest at the level of the valve The C arm is returned to the 0 degree position (vertical) and the patient is moved horizontally out of the field of the x ray image A square centimeter grid is then placed at the level of the mitral valve and an x ray is taken The patient is moved back into the x ray image and a photo is obtained of the ball valve When the data was analyzed this information was used for measuring the ball diameter and therefore the scale factor of each photo That is, as described above the scale factor for each subsequent photo is not the same the ball diameter is measured in each photo and is used to establish the scale factor

Fig 2 illustrates the measurement procedure employed in the analysis of a single photo The photograph distances R_1 and R_2 were measured as well as the photograph ball diameter D (averaged in two directions) Since the actual diameter of the ball is known from the grid measurement (call this diameter D_{ef}) the physiological distance is

$$\text{physiological } R_1 = R_1 D_{ef}/D \quad (1)$$

and

$$\text{physiological } R_2 = R_2 D_{ef}/D \quad (2)$$

These two components constitute the vector $\overline{M}$ described below

The patient was placed in one of six positions on right side (90 degrees rotation about longitudinal axis) right back (45 degrees rotation) flat on back left back (45 degrees rotation) left side (90 degrees rotation) and tilted head up (30 degrees measured at sternum) For each position three photos were taken at different camera positions In practice these three camera locations were never allowed to be co planar however this is not an essential theoretical restriction but represents a practical consideration of weighting more equally all three dimensions

abc matrix M matrix

$$\begin{pmatrix} 1-a_1^2 & -a_1b_1 & -a_1c_1 \\ -a_1b_1 & 1-b_1 & -b_1c_1 \\ -a_1c_1 & -b\,c_1 & 1-c_1^2 \\ 1-a_2^2 & -a_2b_2 & -a_2c_2 \\ -a_2b & 1-b_2^2 & -b_2c_2 \\ -a_2c_2 & -b_2c_2 & 1-c_2^2 \end{pmatrix} \begin{pmatrix} x \\ y \\ z \end{pmatrix} = \begin{pmatrix} Mx_1 \\ My_1 \\ Mz_1 \\ Mx_2 \\ My_2 \\ Mz_2 \end{pmatrix} \quad (9)$$

It is desired to minimize the error ϵ^2 of equation (10)

$$\epsilon^2 = \sum_{n=1}^{N} (m - \alpha x - \beta y - \gamma z)^2 \quad (10)$$

where m is defined as the n^{th} element in M matrix ($m_1 = Mx_1$ $m_2 = My_1$ $m_3 = Mz_1$ $m_4 = Mx_2$ etc) α is the n^{th} element of the first row and β is the n^{th} element of the second row and γ the n^{th} element of the third row of the abc matrix

Minimizing equation (10) with respect to x y and results in equation (11) after some re arrangement

$$x\sum^{N}_{n=1}\alpha^2 + y\sum\alpha_n\beta + z\sum\alpha\gamma = \sum\alpha m$$

$$x\sum^{N}_{n=1}\alpha_n\beta + y\sum\beta + z\sum\beta\gamma = \sum\beta m$$

$$x\sum^{N}_{n=1}\alpha\gamma + y\sum\beta\gamma + z\sum\gamma^2 = \sum\gamma_n m \quad (11)$$

This equation contains 3 unknowns (x y z) which can now be solved by standard techniques This results in a solution to equation (8) in terms of the solution generating the minimum mean square error

In addition to the results x y z being printed out the rms error (ϵ^2 [N − 1]$^{1/2}$ is also calculated This has proved invaluable in detecting data handling blunders (e g misplaced decimal point misreading 2 for 3 4 for 9 etc) and is a measure of the confidence one may place on the result

V *Summary of methodology* A computer program was written according to the outline given below

A READ DATA
  1 patient position (γ) x or y axis rotation
  2 number of photos analyzed for a given patient position
  3 arm and table angles
  4 photo distance measurements

B PRELIMINARY CALCULATIONS
  1 camera location with respect to patient coordinates
  2 M coefficient matrix equation (9)
  3 abc coefficient matrix equation (9)
  4 coefficients for 3 x 3 matrix equation (11)

C MATRIX SOLUTION
  1 solve equation (11)

D OUTPUT
  1 x y z coordinates
  2 $(\epsilon^2/(N-1))^{1/2}$
  3 % error

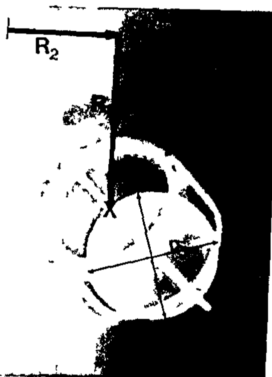


Fig. 2. An example of a photo of the artificial mitral valve together with distance measurements made from the photo. The large X is the midsternum marker.

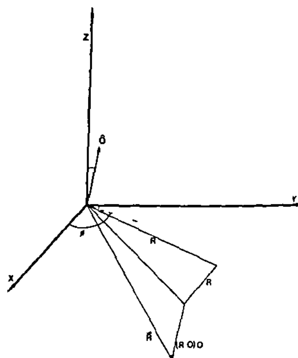


Fig. 3. Patient coordinate system used in the analysis of the data. The origin is at the midsternum marker. The +x axis points towards the feet, +y axis towards the left arm, and +z axis out of the thorax.

system. More briefly this can be written as equation (5) where the coefficients a, b, and c are defined by equations (3) and (4). This camera location is illustrated in Fig. 3.

$$\hat{O} = a\imath + b\jmath + ck \qquad (5)$$

The mitral valve position is defined by another vector R

$$\vec{R} = x\imath + y\jmath + zk \qquad (6)$$

as described in Fig. 3. x, y, and z are the actual physiological distances along the unit vectors defining valve location.

Viewing from the camera location $\hat{O}$, a two dimensional vector $\vec{M}$ is presented which is the measured heart position as seen from a single x-ray photo. $\vec{M}$ is given by the vector equation

$$\vec{M} = \vec{R} - (\vec{R} \cdot \hat{O})\,\hat{O} \qquad (7)$$

In order to obtain the third dimension (which is co-linear with $\hat{O}$) at least one other photo from a different observer position must be obtained. These different camera positions will be denoted by subscripts 1, 2, etc. (in practice 3 different observer angles were used to allow for the contingency of some photos being spoiled during exposure or processing). The equations which must be solved to determine heart position is summarized by equations (8).

$$\vec{M}_1 = \vec{R} - (\vec{R} \cdot \hat{O}_1)\,\hat{O}_1$$
$$\vec{M}_2 = \vec{R} - (\vec{R} \cdot \hat{O}_2)\,\hat{O}_2$$

$$\vdots$$

$$\vec{M}_n = \vec{R} - (\vec{R} \cdot \hat{O}_n)\,\hat{O}_n \quad n \geq 2 \qquad (8)$$

For $n \geq 3$ these equations appear to over-specify the problem and additional photos (more than 2) would not appear to be necessary nor desirable. In fact, given actual patient data no exact solution to equations (8) exists due to various combinations of measurement and round-off errors and actual motion of the heart. Given this fact, a solution is sought on the basis of minimum least squares error. This criterion can, of course, be applied to two photos, but greater confidence in the result is obtained with a larger number.

Expressing equations (8) in matrix notation results in equation (9).

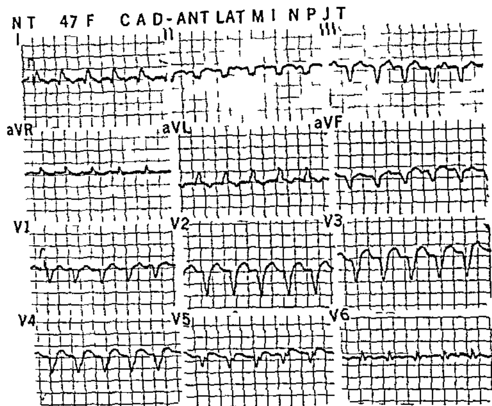


Fig 1 Twelve-lead electrocardiogram recorded in a 47 year-old woman with sinus tachycardia A V dissociation NPJT (rate = 154 per minute) and an acute anterior wall myocardial infarction The QRS complexes are prolonged at 0 13 second their appearance was identical during intact A V conduction

and 18 women whose ages ranged from 41 to 87 years with a mean age of 64 years When subdivided according to location of infarction as determined by usual electrocardiographic criteria there were 24 cases of inferior wall infarction (50 per cent) 16 cases of anterior wall infarction (33 3 per cent) and eight cases of infarction at other sites (posterior isolated lateral 16 5 per cent) Congestive heart failure was classified as mild when there were bibasilar rales without dyspnea moderate when rales were heard over the entire lower half of the anterior and posterior thorax and severe in the presence of pulmonary edema Patients with significant diminution of blood pressure in the absence of any acute postural change or administration of narcotics were classified as having either hypotension (a decline of brachial blood pressure greater than 20 mm Hg in systolic and diastolic levels) or shock when the drop in blood pressure was accompanied by cold diaphoretic extremities a weak pulse and a decline in urinary output In those cases where the electrocardiographic differential diagnosis was accelerated ventricular rhythm vs NPJT with aberrant ventricular conduction the latter diagnosis was accepted only if there were identifiable sinus capture beats with QRS complexes identical with those seen during the tachyarrhythmia Only four cases fell into this latter category Significance of the difference between mean values was determined using Student s t test

Results

Type of non paroxysmal A V junctional tachycardia The most prevalent form of NPJT was not associated with identifiable independent atrial activity (28 cases 58 per cent) The balance of the types of NPJT encountered were as follows complete A V dissociation (six cases 12 5 per cent Fig 1) incomplete A V dissociation

Non-paroxysmal A-V junctional tachycardia associated with acute myocardial infarction

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Non-paroxysmal A-V junctional tachycardia (NPJT) results from an acceleration of impulse formation at the region of the A-V junction.[1] This tachyarrhythmia is usually associated with digitalis toxicity, acute rheumatic fever, or inferior wall infarction,[1] and generally produces a ventricular rate of 60 to 150 beats per minute.[2] Despite existing evidence that this dysrhythmia does not per se indicate a poor prognosis in the setting of acute myocardial infarction,[1,3] a recent study has demonstrated a high mortality rate in subjects with acute infarction and NPJT.[2] Since our impression, based on clinical experience, did not correspond with that of the recent study, we reviewed electrocardiographic findings and clinical outcome in a group of patients with NPJT which occurred in the setting of acute myocardial infarction.

Materials and method

The records of all subjects who were admitted to the Good Samaritan Hospital with the provisional diagnosis of acute myocardial infarction during the years 1970 and 1971 were reviewed. These years were selected because of the profusion of rhythm strips added to permanent clinical records during admission to the Coronary Care Unit. Patients were accepted as having acute myocardial infarctions when their electrocardiograms demonstrated classical significant Q waves with evolving S-T segment and T wave changes compatible with that diagnosis associated with a history of at least one hour of retrosternal chest pain. Furthermore, all subjects had serial elevations of serum glutamic oxaloacetic transaminase (SGOT) to at least twice control levels. The normal range for SGOT at this institution is 0 to 50 I.U. Based on the above criteria, 494 patients had acute myocardial infarction. Of these, 48 subjects (9.7 per cent) had NPJT. The records of these patients were reviewed specifically for the purpose of determining survival, peak SGOT level, ventricular rate during NPJT, day of occurrence of the tachycardia, and symptoms produced by it. Subjects with evidence of digitalis toxicity and those who were receiving atropine or adrenergic stimulating drugs prior to the onset of the tachyarrhythmia were excluded from the study. There were 30 men

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course of acute myocardial infarction was significantly higher in those patients who died (survivors 152 ± 114 non survivors 488 ± 519 P < 0 01)

Onset of NPJT and relationship to symptoms In the vast majority of cases (84 per cent) NPJT appeared during the first three days of hospitalization The time of onset in the non survivors paralleled that of the entire study group with 80 per cent of cases manifesting this arrhythmia during the initial 72 hours of observation No episode of acute pulmonary edema hypotension or shock was produced or worsened by the occurrence of NPJT Mild to moderate congestive heart failure occurred as a direct consequence of NPJT in six subjects The respective locations of infarction in this latter group were three cases—anterior three cases—inferior The average ventricular rates in these six patients tended to be higher (mean—132 per minute) than rates in those subjects in whom symptoms were not evoked by NPJT (mean—90 per minute)

Discussion

The underlying basis of accelerated A V junctional discharge associated with acute myocardial infarction is not well established[3] Local effects of increased catecholamine and potassium levels[2] have been advanced as possible reasons for increased A V junctional automaticity in the setting of acute infarction yet there is no substantial proof for such operative mechanisms The incidence of NPJT in acute infarction and the relative distribution of anatomic sites described in this study is comparable with the data of Konecke and Knoebel[2] who found 10 per cent of 203 subjects with coexisting acute infarction and NPJT

Furthermore NPJT occurred almost twice as frequently with inferior wall as compared with anterior wall infarction in their study Examination of the respective mortality rates described by Konecke and Knoebel and those set forth herein differ in that we found only a single subject with inferior wall infarction and NPJT who died In contrast the other authors described a mortality rate of 43 per cent under similar circumstances In general a poor prognosis can be assigned to those subjects with anterior wall infarction and NPJT since the mortality rate in patients with this combination of findings was previously found to be almost 100 per cent[2] and was 62 per cent in this study

In our experience NPJT per se rarely produces a change in the clinical status of subjects with acute myocardial infarction The major determinants for ultimate clinical outcome appear to be the ventricular rate during NPJT and peak SGOT level It is possible that the more rapid ventricular rates associated with NPJT increased the extent of myocardial damage[4] and consequently the mortality rate due to shock power failure asystole and secondary ventricular fibrillation Alternatively the more rapid AV junctional discharge rates may have been a reflection of greater underlying myocardial necrosis The presence of significantly higher peak SGOT levels in those patients with NPJT who succumbed is in accord with recent evidence which suggests that in general the extent of myocardial infarction can be grossly reflected by the magnitude of serum enzyme rise[5] Over all mortality rates during acute infarction appear to have a highly significant linear correlation with the SGOT level[6] If these observations apply to the data presented in this study then it could be surmised that the extent of myocardial necrosis in patients with anterior wall infarction and coexisting NPJT was of a greater magnitude than that in subjects with inferior wall infarction and identical dysrhythmias Detailed clinicopathologic study appears necessary in order to shed light on this possibility

In conclusion NPJT does not necessarily indicate a poor prognosis in the setting of acute myocardial infarction Our data do suggest however that the mortality rate in subjects with coexisting NPJT and anterior wall infarction is high

Summary

The hospital records of 48 subjects with acute myocardial infarction complicated by non paroxysmal A V junctional tachycardia (NPJT) were reviewed Fifteen of 48 subjects (31 per cent) so affected died NPJT was most commonly associated with inferior wall infarction (24/48 50 per cent)

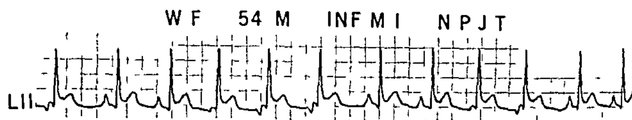


Fig. 2. Variations of P wave configuration noted in a 54-year-old man with acute inferior wall myocardial infarction prior to established NPJT. Lead II rhythm strip demonstrates gradual change in P wave polarity from upright to total inversion.

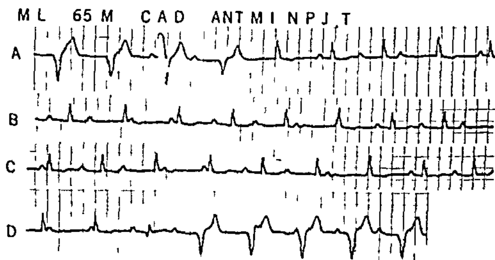


Fig. 3. *A* through *D*. Lead II rhythm strip from a 65-year-old man with an acute anterior wall myocardial infarction: sinus rhythm, complete A-V block, NPJT (rate = 70 per minute), and intermittent accelerated ventricular rhythm. Widened negative QRS complexes occur at the beginning of record *A* and end of record *D*; their intrinsic rate is slightly more rapid than that of the NPJT. Fusion beat (fourth QRS complex in record *A*; third QRS complex in record *D*) can be seen. The wide QRS complexes presumably arise from an accelerated ventricular (or fascicular) subsidiary pacemaker which usurps control of the ventricles.

(seven cases, 14.5 per cent), wandering atrial pacemaker (five cases, 10.5 per cent, Fig. 2), and retrograde A-V junctional Wenckebach phenomenon (two cases, 4 per cent). In a single patient apparent episodes of accelerated ventricular rhythm occurred in the setting of complete A-V block and NPJT (Fig. 3). There was no relationship between the site of infarction and the type of NPJT. Furthermore, the variations of NPJT did not correlate with survival.

Mortality and relation to site of infarction. Of 48 patients, 15 died (31 per cent). Ten of 16 subjects (62.5 per cent) with anterior wall myocardial infarction died during the course of NPJT. On the other hand, 23 of 24 patients (96 per cent) with inferior wall infarction survived. Four of eight (50 per cent) subjects with infarctions at other sites died. There were no significant differences between the mean ages or number of previous infarctions in the survivor and non-survivor groups.

Ventricular rate. Mean (± 1 standard deviation) heart rates during NPJT in patients with inferior and anterior wall myocardial infarctions were 85.4 ± 28.1 and 113.4 ± 35.3 beats per minute, respectively. The difference between these values was statistically significant ($P < 0.01$). Six of ten patients (60 per cent) with anterior wall myocardial infarction who died had ventricular rates greater than 100 per minute during NPJT. The only subject with inferior wall infarction who did not survive had a heart rate of 110 per minute. Nine of all 15 subjects (60 per cent) who died manifested rates equal to or greater than 100 per minute during NPJT.

Peak SGOT levels. The mean value for peak SGOT level obtained during the

Clinical diagnosis of persistent left superior vena cava by observation of jugular pulses

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The persistence of the left superior vena cava (LSVC) is a congenital anomaly of the coronary sinus usually draining through this vessel It has no hemodynamic importance [1-4] In 3 to 4 per cent of the cases it is an association of other congenital cardiovascular malformations [4] The persistence of LSVC may be important for the surgeon because it requires special handling in extracorporeal circulation [1]

Generally the diagnosis is made by intra cardiac catheterization or by surgery The possibility of a clinical diagnosis on the basis of the radiological appearance [2,4,6] and by the deviation of the mean electrical axis of the P wave toward the left has been reported [4,7,9]

In 1967 Colman[10] described a case in which the pulse of the left jugular vein was more prominent than that of the right one and this was considered a sign of per sistence of LSVC This finding has not been mentioned again in the literature For this reason we investigated it in patients in whom the malformation was proved in an attempt to elicit its usefulness and inci dence

Methods

The study included six patients in whom an LSVC had been demonstrated by intra cardiac catheterization or at surgery and a seventh case with mirror image dextro cardia with situs inversus and persistent right superior vena cava A difference in the amplitude of the external jugular pulses in both sides of the neck was looked for The jugular phlebogram was recorded subse quently using a four channel jet inscription poligraph (Mingograph 34 Elema Schonan der) Simultaneous recording of an ECG lead and a phonocardiogram with micro phone EMT 25 and logarithmic filter were obtained The pressure phlebogram was inscribed with a Boucke Brecht Infraton receptor [11] with linear response of 0 02 to 200 Hz following the technique described by Hartmann [12] The receiver was held with a pneumatic cuff with a variable pressure of 2 to 10 mm Hg Simultaneous phlebo graphic bilateral recordings were obtained when possible otherwise the same pressure was applied in each one of the recordings The same procedure was used in three pa tients without the anomaly The paper

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Although ten of 16 (63 per cent) patients with acute anterior wall infarction and NPJT died 23 of 24 patients with acute inferior wall myocardial infarction survived Mean heart rates during NPJT were significantly greater in subjects with anterior wall infarction (113 4 ± 35 3 vs inferior wall 85 4 ± 28 1 P < 0 01) Peak SGOT levels were significantly higher in those patients who died (488 ± 579 vs survivors 152 ± 114 P < 0 01) NPJT altered the clinical status of only six subjects It is concluded that NPJT indicates a poor prognosis in subjects with acute anterior wall infarction but is generally associated with a benign clinical course in patients with inferior infarction These differences may be based on a greater extent of myocardial damage in the former group

We wish to acknowledge the technical assistance of Nancy Copeland R N Carole Crevier Larry Kuriger Sydney Peebles Sharon Squire and Les Zendle

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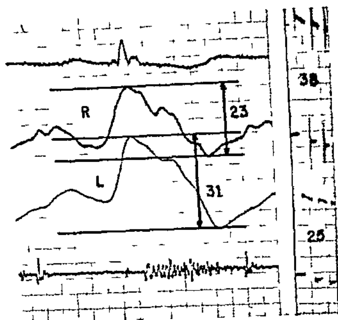


Fig 1 Jugular phlebogram of Case No 1 Note that the height of the phlebogram has been corrected in the table according to the amplification (ECG Lead II and phonocardiogram are on top and bottom Numbers represent mm)

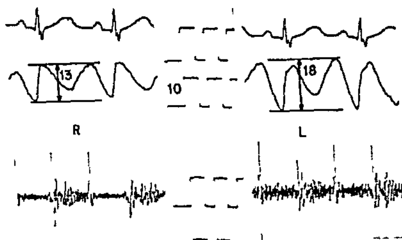


Fig 2 Jugular phlebo ram of Case No 2 (see Table I) (ECG lead and phonocardiogram are on top and bottom Numbers represent mm)

catheterization does not always elicit the malformation only 68 to 90 per cent of the cases are diagnosed Its clinical diagnosis would prompt the intentional searching by catheterization or anticipate its existence thus preventing unexpected shortcomings such as technical surgical problems or other problems in the introduction of a pacemaker electrode by a peripheral vein through the left arm[4] and in modifying techniques of cannulation for extracorporeal circulation[1]

Persistence of LSVC has been anticipated from the radiological image in 39 to 86 per cent of the cases[4 6 11]—i e a visible shadow to the lef of the cardiac contour The left axis deviation of the P wave in 34 to 70 per cent of the cases[4 7 9] is another useful indication

The description by Colman[10] of the

Table I. Patient data and relationship between left and right phlebograms

Case	Age yr	Sex	Diagnosis	Diagnosis L.S.V.C.*	Height of jugular phlebogram (mm.) Left	Height of jugular phlebogram (mm.) Right	Left/right ratio
1	17	F	Dextroversion in situs solitus. Complete transposition of the great arteries with ventricular inversion. Pulmonary stenosis, ventricular septal defect. L.S.V.C. to C.S.	C	12.4	6	2
2	4	M	Atrial septal defect with pulmonary stenosis. Patent ductus arteriosus (operated). L.S.V.C. to C.S.	S	18	13	1.3
3	5	F	Aortic incompetence and ventricular septal defect, pulmonary stenosis. L.S.V.C. to C.S.	C. S.	17.5	12.2	1.43
4	7	F	Ventricular septal defect. Pulmonary hypertension. L.S.V.C. to C.S.	C. S.	15	9	1.66
5	4	M	Transposition of the great arteries. Double outlet right ventricle. Pulmonary stenosis. Ventricular septal defect. Atrial septal defect. L.S.V.C. to C.S.	C	8.9	5.2	1.7
6	3	F	Double outlet right ventricle. *Atrio ventricularis communis*. L.S.V.C. to C.S.	C	13	19	1.46
7	8	F	Mirror image dextrocardia, situs inversus. Patent ductus arteriosus, ventricular septal defect, atrial septal defect. R.S.V.C. to C.S.	C	20	32	0.62†

*Abbreviations: L.S.V.C. = left superior vena cava; R.S.V.C. = right superior vena cava; C.S. = coronary sinus; C = catheterization; S = surgery.
†See text for explanation.

recording speed was 50 to 100 mm. per second.

The distance from the peak of the a wave to the lowest point, usually the x collapse, was measured in each tracing. The height of the c wave was not measured since it is influenced by the pulse of the carotid artery. The height was adjusted by the amplification with the following formula:

$$\frac{\text{Height of phlebogram in mm.} \times 10}{\text{Amplification in mm.}}$$

A left/right phlebogram ratio was calculated as follows:

$$\frac{\text{Height of left phlebogram}}{\text{Height of right phlebogram}}$$

Results

Age, sex, and associated heart disease of the cases are summarized in Table I. In six of the seven cases the left jugular pulse had greater amplitude on visual inspection than the right one and the left/right phlebogram ratio exceeded one. In the seventh case, the right jugular pulse had greater amplitude demonstrated with phlebographic tracings. This patient had mirror image dextrocardia with situs inversus—i.e., there was an anomalous right superior vena cava. The three control patients showed a larger right phlebographic tracing with a left/right ratio of 0.15, 0.25, and 0.42, respectively.

The different values of the phlebographic tracings and the relation between the left and right phlebograms are described in Table I. Figs. 1, 2, and 3 are examples of this condition.

Discussion

The importance of the dia[illegible]nosis of LSVC has been emphasized[1,2] [illegible] acardiac

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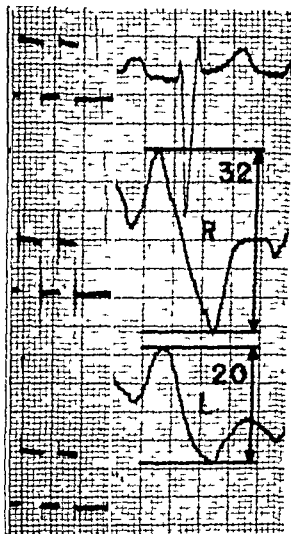


Fig 3 Jugular phlebogram of Case No 7 The right pulse is of greater amplitude but the patient has *situs inversus with persistent right superior vena cava* (See table and text ECG Lead II is on top Numbers represent mm)

greater amplitude of the left jugular pulse in a proved case with LSVC was observed and demonstrated in all our cases The prominence of the right jugular pulse in the patient with dextrocardia and situs inversus is considered positive on account of the expected inversion and this allows us to consider a new clinical evidence probably more consistent *in the diagnosis* of this anomaly

The mechanisms advocated by Colman[10] explain the greater amplitude of the left jugular pulse Normally the right jugular pulse is either equal or even higher than the left one as is shown *in our controls* This is due to the fact that the right venous system of the neck is in a relatively straight communication with the right atrium whereas the left internal jugular vein communicates with the superior vena cava via a longer and nearly horizontal channel [10] In the presence of persistent LSVC the participation of the coronary sinus during atrial systole or the greater atrial pressure *on the coronary sinus may transmit the* pressure wave better toward the venous system in the left side and pressure measurements on both superior vena cavae when coexisting should be performed to assess the hypothesis

The greater amplitude of the left jugular pulse can be found in other circumstances The obstruction or absence of the right superior vena cava can decrease the pres*sure in the homolateral jugular* vein enough to make the pulse unequal[10] phasic or expiratory obstruction of the left innominate vein by an uncoiled aortic arch can increase the pressure in the internal jugular vein [14] as is seen in elderly and arteriosclerotic patients The compression of the venous system of the left side by neoplastic processes of the superior mediastinum can also increase the venous pressure of the same side Finally anomalous drainage of the pulmonary veins to the left innominate vein sometimes associated with persistent LSVC, could increase the amplitude of the left jugular pulse These situations can be suspected by other signs and so the differ*ential diagnosis is easily done*

Summary

In seven patients with persistent left superior vena cava (LSVC) diagnosed at surgery or by intracardiac catheterization the difference in amplitude between the left and the right jugular pulses was investigated In six cases the left jugular pulse had greater amplitude and in the seventh case the opposite was true but this patient had mirror image dextrocardia with situs inversus and therefore it was considered a *positive sign The greater amplitude of the* jugular pulse in the same side of the anomalous superior vena cava (usually the left) appears to be a useful sign to suspect the diagnosis of this malformation

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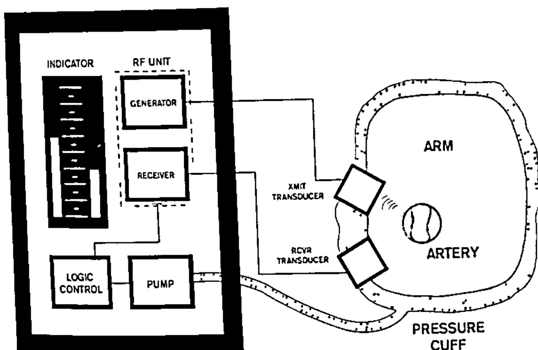


Fig 1 Principle of operation of the automatic Doppler ultrasound blood pressure system Ultrasonic energy is generated and transmitted via the transmitter transducer into the arm toward the brachial artery Reflected waves are sensed by the receiver transducer and receiver An occlusive cuff is inflated to above systolic then slowly deflated Systolic and post systolic arterial wall motion is sensed by the logic as a change (Doppler shift) in the frequency of the reflected wave The logic determines systolic and diastolic pressures and displays them on the indicator

sures (Fig 1) An occlusive cuff is placed on the arm in the usual manner with an ultrasonic transducer on the arm over the brachial artery Upon operator activation of the system the cuff is inflated automatically to a preset pressure and deflated at the rate specified by the American Heart Association[8] A low energy* ultrasonic field is transmitted into the arm the portion of the ultrasound that is reflected by the arterial wall shifts in frequency (Doppler shift) when the wall of the artery moves Above systolic the vessel remains closed due to the pressure of the occluding cuff and motion signals are not received As cuff pressure falls to the point where it is just overcome by brachial artery pressure the artery wall snaps open This opening wall movement often corresponding to the occurrence of the first Korotkoff sounds[1] produces a Doppler shift which is interpreted after several checks by logic in the instrument as systolic and causes a mercury column to lock in place at the indicated pressure As cuff pressure declines further the instrument continues to analyze ultrasound reflected from the arterial wall At a point corresponding to the fourth phase of Korotkoff sounds (muffling) the violence of wall motion markedly diminishes[5] The instrument notes the sudden diminution in the amplitude of the Doppler shift and cuff pressure at this point is displayed as diastolic pressure The system is totally automatic The operator positions the cuff/transducer assembly pushes a button and reads the results

*<50 mW/cm.²

Since the use of Doppler ultrasound blood flow detectors in the measurement of BP has also been reported[9-11] the similarities and differences in the two ultrasonic approaches should be briefly noted Both depend on motion detection by Doppler shift during cuff deflation In a

Automatic ECG and blood pressure measurement in multitesting Correlation of blood pressure and ECG abnormalities

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*M L D George B S E E***
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Cranbury N J

Large health testing demonstrations allow rapid large scale testing of new concepts and instruments as well as extraction of new data inter relations Previous demonstrations had been used to develop and validate on line computer electrocardiogram (ECG) analysis and derive ECG classifications[1-4] This report describes the inter relations of these ECG classifications with automatically derived blood pressure The 1 108 participants in the American Dental Association Annual Health Evaluation Program (1970) had the following tests an automated ECG by the Medical Systems Development Laboratory Program[1-4] automatic blood pressure measured with an instrument approaching intra arterial pressure in accuracy[5-7] clinical chemistry (blood urea nitrogen blood glucose serum cholesterol and uric acid) tonometry head, neck, and oral examination and x ray examination of teeth jaws and chest

The results showed blood pressures were distributed in a manner similar to the U S population and ECG classifications were similar to those reported in prior multitesting of this group There is strong linear relation between the per cent of questionable ECG s and the systolic and diastolic pressures Expected correlations between age and QRS axis and pressure and ECG wave form amplitudes were not found

System description

The ECG system has been described in detail[2] The blood pressure (BP) measurement system is an ultrasonic device capable of sensing arterial wall motion combined with a computer that analyzes the wall motion signals to detect systolic and diastolic and display the corresponding pres

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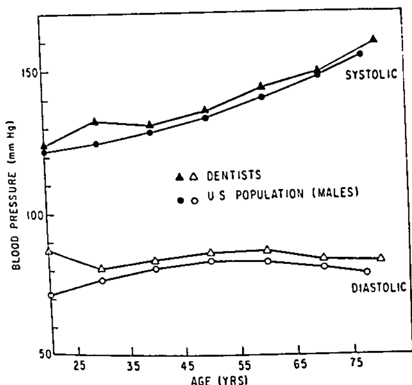


Fig 2 Blood pressures obtained at the 1970 Health Evaluation Program as compared to the U S population Systolic and diastolic pressures closely paralleled the U S population except in the younge t group which cont ined only one subject The slight difference in absolute values may be due to the difference in instruments used or observer variation This difference is probably not clinically significant

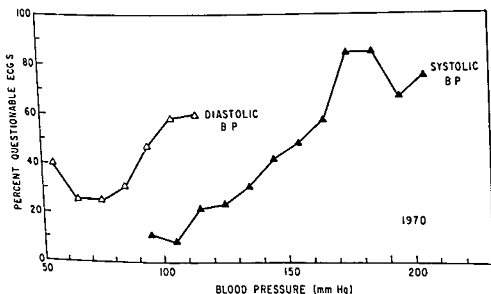


Fig 3 Relat on of p oport on of questionable ECG s to systol c and diastolic blood pressure The percentage of questionable ECG s rises smoothly w th both sy tol c and diastol c blood pressures plateauing well in the hyperten ve range The e are no defin te breaks until the plateau the proportion rising constantly with blood pres re.

Table I. Weight, blood pressure, and ECG findings in American Dental Association screening

Age (yr)	No	Mean weight (kg)	Hypertension				ECG questionable	
			Systolic		Diastolic			
			No	%	No	%	No	%
0-24	1	71.3	0	0	0	0	0	0
25-34	156	81	15	10	2	1	36	23.1
35-44	293	81	29	10	16	8	64	21.8
45-54	344	80	57	17	30	9	116	33.7
55-64	193	80	61	32	12	6	98	50.7
65-74	105	79	44	42	10	9	56	53.4
75-84	16	72.3	10	62	0	0	10	62.5
Total (mean) 47.5	1,108	—	216	19.5	70	6.9	380	34.4

blood flow detector, the ultrasonic frequency is set to produce a signal ascribed to backscattering from moving blood cells.[10] This instrument, however, uses lower ultrasonic frequency to reduce blood flow backscatter, filters out the higher frequency reflections and passes the lower frequencies, thus following movement of the relatively slow moving arterial wall. Clinically, the major apparent difference is a reported inability of the blood flow detectors to obtain diastolic pressures in some patients during shock[10] and in smaller infants.[11] However, as previously described, this instrument is an automated system and thus has advantages in screening applications where rapidity and avoidance of observer bias and fatigue are important considerations.

Method

Participants in the American Dental Association Convention (1970) were invited to the Annual Health Evaluation Program, a series of health tests. The tests included an automated electrocardiogram by the Medical System Development Laboratory Program,[1-4] automatic BP with the instrument described above, clinical chemistry (blood urea nitrogen, blood glucose, serum cholesterol, and uric acid), tonometry, neck, and oral examination and x-ray examination of teeth, jaws, and chest. The ECG had been automatically analyzed at the Health Evaluation Program in previous years by the same program reported here. Results have been reported elsewhere.[4,5]

To facilitate rapid recording of BP, two tables were prepared with the system cuff, transducer, and cables appropriately positioned and fastened for rapid application and removal. The operators had no previous knowledge of or experience in BP measurement and were easily trained. Computer ECG analyses were reviewed and were classified into normal and questionable based on previously reported criteria[5] by one of the authors (C. A. Caceres).* Participants' BP, age, height, weight, and ECG results were recorded. Results were subjected to computer analysis.

Timing of the blood pressure analysis portion of the exam showed that each participant was processed in an average time of 45 seconds. Each of the two instru-

*Electrographic interpretations were classified as "normal" or "questionable" without knowledge of history, age, sex, or physique of the participant. Tracings were considered normal if the following conditions were met: (1) the QRS axis was between −19 degrees and +95 degrees; (2) the heart rate was between 56 and 109 beats per minute; (3) no more than one minor abnormality was found (e.g., minimal ST depression, horizontal QRS, abnormal P wave axis, etc.); or (4) no arrhythmia was present. The others, the questionable ECG's, had findings probably of clinical significance.

Individual blood pressures are usually not considered hypertensive until a level of > 150 mm Hg systolic or > 100 mm Hg diastolic has been attained These results showed 19 per cent with systolic and 6 9 per cent with diastolic hypertension The U.S figures based on a lower average age are 17 per cent and 5 5 per cent [12]

The differences from the U S population mean for each age group are well within the bounds of observer variation[14 15] and are thus probably not clinically significant The small consistent difference noted may be due to the use of the more sensitive ultrasound method or to the activity of subjects attending a meeting

As expected the blood pressure level rose with age but the body weight did not The percentage of questionable ECG s is similar to previously reported data on a similar population of dentists[1 4 5] These data indicate that the population screened at the 1970 Annual Health Evaluation is representative of the U S male population with respect to blood pressure We believe from unpublished data (C A Caceres) that this applies to the ECG as well

The almost linear relation of the proportion of questionable ECG s to BP was not expected Another unexpected finding was the lack of correlations of age and BP with the ECG changes they are usually associated with Review of the age and BP distribution shows the number of extreme cases may be too small to allow this correlation to become clear Nonetheless the ECG does change with BP but in a non specific way

Summary and conclusion

An automatic ultrasound blood pressure instrument was used to measure blood pressure (BP) and a computer was used to analyze ECG s in 1 108 male professionals at a voluntary Health Evaluation Program at a professional society meeting BP s were recorded with the technique recommended by the American Heart Association in an average time of 45 seconds per participant by technicians untrained in the auscultatory method of obtaining BP Nineteen per cent of the participants had systolic hypertension (> 150 mm Hg) and 7 per cent had diastolic hypertension (> 100 mm Hg) The mean BP s and percentage of abnormals were equivalent to the U S population Computer ECG analysis showed 34 4 per cent questionable findings consistent with previous experience The study showed a strong positive linear relation hip between the proportion of questionable ECG s and the systolic and diastolic blood pressure

The author wish to thank Mr H C Chang and Mr C Rosencrown Roche Medical Electronic who performed the statistical analyses presented here

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Table II Relation of blood pressure to ECG

Systolic B P		Questionable ECG		Diastolic B P		Questionable ECG	
(mm Hg)	No	No	%	(mm Hg)	No	No	%
91 100	9	1	11	51 60	10	4	40
101 110	44	4	9	61 70	102	26	26
111 120	149	33	22	71 80	321	84	26
121 130	250	61	24	81 90	399	125	31
131 140	242	76	31	91 100	206	99	48
141 150	198	83	42	101 110	54	32	59
151 160	120	56	48	111 120	15	9	60
161 170	50	29	58	121 130	1	1	(100)
171 180	20	17	85				
181 190	13	11	85				
191 200	9	6	67				
201	4	3	75				
Total	1 108	380	34 4		1 108	380	34 4

ments was used on 600 participants without failure

There were 1 108 male participants in the screening program For each age category the mean weight number of systolic and diastolic hypertensives and number with abnormal ECG s were tabulated (Table I)

Results

The 1 108 participants had a mean age of 47 5 years Of the 1 108 participants tested 19½ per cent had systolic hypertension (> 150 mm Hg) and 6 9 per cent had diastolic hypertension (> 100 mm Hg) Thirty four per cent had questionable electrocardiograms The per cent of hypertensives and abnormal ECG s increased with age Comparison of mean systolic and diastolic BP by age groups with the U S population[12] shows the participants to be representative of the population although both systolic and diastolic tended to be a few mm Hg elevated (Fig 2) The level of systolic and diastolic pressures were closely related to the percentage of questionable ECG s (Table II and Fig 3) The proportion of questionable ECG s rose smoothly with the level of blood pressure No distinct 'break point was evident at any level A similar rise occurred with age (Table I)

Regression analyses were done between ECG measurements and the following systolic and diastolic BP age and ponderal index Correlations were attempted with P wave amplitude (A) in II aVL, V_2 and V_5 Q wave A in II aVL and V_5 Q wave duration (D) in II aVL and V_5 R wave A in II aVL and V R V_5 A + S A in V_1 and V_2 T wave A II aVL V V_5 PR II QRS D II QRS frontal plane axis ST T angle and QRS T angle Regression analyses were also performed between heart rate and age BP PR QRS D in II QRS axis ST T angle and QRS T angle No significant correlations were found

Discussions and conclusions

Blood pressure is one of the more important prognostic measurements in health evaluation Manual cuff stethoscope methods have inherent limitations including observer variation which may be severe[13,15] the requirement for trained personnel and the development of fatigue during prolonged health testing Automatic methods offer reproducibility and accuracy and are indefatigable The instrument used in this study has been evaluated for accuracy[5,7] This study demonstrates that accurate results may be obtained rapidly by personnel without training in the cuff stethoscope method

Individual blood pressures are usually not considered hypertensive until a level of > 150 mm Hg systolic or > 100 mm Hg diastolic has been attained. These results showed 19 per cent with systolic and 6.9 per cent with diastolic hypertension. The U.S. figures based on a lower average age are 17 per cent and 5.5 per cent.[13]

The differences from the U.S. population mean for each age group are well within the bounds of observer variation[14,15] and are thus probably not clinically significant. The small consistent difference noted may be due to the use of the more sensitive ultrasound method or to the activity of subjects attending a meeting.

As expected, the blood pressure level rose with age but the body weight did not. The percentage of questionable ECG's is similar to previously reported data on a similar population of dentists.[1,4,5] These data indicate that the population screened at the 1970 Annual Health Evaluation is representative of the U.S. male population with respect to blood pressure. We believe from unpublished data (C. A. Caceres) that this applies to the ECG as well.

The almost linear relation of the proportion of questionable ECG's to BP was not expected. Another unexpected finding was the lack of correlations of age and BP with the ECG changes they are usually associated with. Review of the age and BP distribution shows the number of extreme cases may be too small to allow this correlation to become clear. Nonetheless, the ECG does change with BP but in a non-specific way.

Summary and conclusion

An automatic ultrasound blood pressure instrument was used to measure blood pressure (BP) and a computer was used to analyze ECG's in 1,108 male professionals at a voluntary Health Evaluation Program at a professional society meeting. BP's were recorded with the technique recommended by the American Heart Association in an average time of 45 seconds per participant by technicians untrained in the auscultatory method of obtaining BP. Nineteen per cent of the participants had systolic hypertension (> 150 mm Hg) and 7 per cent had diastolic hypertension (> 100 mm Hg). The mean BP's and percentage of abnormals were equivalent to the U.S. population. Computer ECG analysis showed 34.4 per cent questionable, a finding consistent with previous experience. The study showed a strong positive linear relationship between the proportion of questionable ECG's and the systolic and diastolic blood pressure.

The author wish to thank Mr. H. C. Chin and Mr. C. Rosen of Brown Roche Medical Electronics who performed the statistical analyses presented here.

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Table II Relation of blood pressure to ECG

Systolic B P		*Questionable ECG*		*Diastolic B P*		*Questionable ECG*	
(mm Hg)	*No*	*No*	*%*	*(mm Hg)*	*No*	*No*	*%*
91 100	9	1	11	51 60	10	4	40
101 110	44	4	9	61 70	102	26	26
111 120	149	33	22	71 80	321	84	26
121 130	250	61	24	81 90	399	125	31
131 140	242	76	31	91 100	206	99	48
141 150	198	83	42	101 110	54	32	59
151 160	120	56	48	111 120	15	9	60
161 170	50	29	58	121 130	1	1	(100)
171 180	20	17	85				
181 190	13	11	85				
191 200	9	6	67				
201	4	3	75				
Total	1 108	380	34 4		1 108	380	34 4

ments was used on 600 participants without failure

There were 1 108 male participants in the screening program For each age category the mean weight number of systolic and diastolic hypertensives and number with abnormal ECG s were tabulated (Table I)

Results

The 1 108 participants had a mean age of 47 5 years Of the 1 108 participants tested 19½ per cent had systolic hypertension (> 150 mm Hg) and 6 9 per cent had diastolic hypertension (> 100 mm Hg) Thirty four per cent had questionable electrocardiograms The per cent of hypertensives and abnormal ECG s increased with age Comparison of mean systolic and diastolic BP by age groups with the U S population[12] shows the participants to be representative of the population although both systolic and diastolic tended to be a few mm Hg elevated (Fig 2) The level of systolic and diastolic pressures were closely related to the percentage of questionable ECG s (Table II and Fig 3) The proportion of questionable ECG s rose smoothly with the level of blood pressure No distinct 'break point' was evident at any level A similar rise occurred with age (Table I)

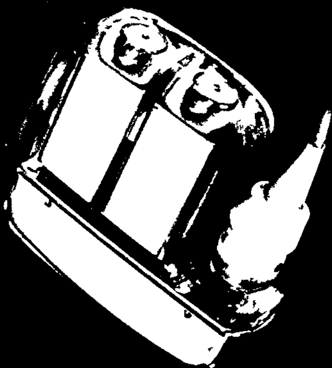
Regression analyses were done between ECG measurements and the following systolic and diastolic BP age and ponderal index Correlations were attempted with P wave amplitude (A) in II aV₁ V₂ and V₅ Q wave A in II aV_L and V₅ Q wave duration (D) in II aV₁ and V₁ R wave A in II aV₁ and V₅ R V₅ A + S A in V₁ and V₂ T wave A II aV₁ V₂ V₆ PR II QRS D II QRS frontal plane axis ST T angle and QRS T angle Regression analyses were also performed between heart rate and age BP PR QRS D in II QRS axis ST T angle and QRS T angle No significant correlations were found

Discussions and conclusions

Blood pressure is one of the more important prognostic measurements in health evaluation Manual cuff stethoscope methods have inherent limitations including observer variation which may be severe[11 15] the requirement for trained personnel and the development of fatigue during prolonged health testing Automatic methods offer reproducibility and accuracy and are indefatigable The instrument used in this study has been evaluated for accuracy[6 7] This study demonstrates that accurate results may be obtained rapidly by personnel without training in the cuff stethoscope method

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Sentry 75
ventricular inhibited pulse generator



GENERAL ELECTRIC

Index to advertisers

implified circuitry or reliability

ew circuit efficiencies hrough the development and daptation of thick film hybrid circuitry born of aerospace technology almost one-half the normal electrical interconnections are eliminated The new circuits improve electrical efficiency *by 45%* (135 micro-watts of power drain vs 244 micro-watts formerly)



The new micro-circuitry in both the sensing and pacing circuits—*plus* the rectangular power cells—allow a 25 / reduction in the volume of the generator Thus while generator size is reduced power capacity is increased 50 %

Hermetic sealing of these critical hybrid circuits *plus* a second overall hermetic sealing of the complete circuitry virt ally locks-out *deteriorative moisture* The metal hermetic containers also provide additional protection from electromagnetic *interference* (EMI)

In addition patient defibrilla tion can be conducted without damaging the generator

Adapts to electrodes

Implant procedures are not altered because the Sentry 75 is compatible with all existing GE electrodes which feature simple self sealing push pull connectors It is also adaptable to the electrodes of other manufacturers

The pulse generator is provided as a bipolar system which at implant can be converted to unipolar pacing if desired This is accomplished by simply removing the *insulating label covering* the metallic plate electrode on the generator s surface and attaching it to a unipolar *electrode or to a bipolar* electrode adapted for unipolar pacing

Standardized output

Choice of rates- Two models of the Sentry 75 pulse generator are presently available with two additional models schedu ed for subsequent availability Models differ only in pacing and hysteresis rates

Model	Pace Rate	Hysteresis (Escape Rate)
A2075A/AD	73	63
A2075B/BD	80	70
A2075C/CD	85	80
A2075D/DD	73	71

A i bl ec d q of 1974

Sentry 75... one generator that meets long-term pacing demands

The Sentry 75 ventricular inhibited pulse generator maximizes the potentials of a proven power source to deliver extended pacing life to most patients regardless of threshold value

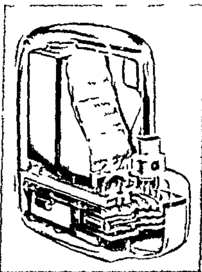
It is General Electric s positive response to the medical profession s demand for a simple extended life pacing system to serve the large majority of patients

The Sentry 75 presents no alterations in implant technique or patient management It is compatible with all GE electrodes and the long reliable service life can be monitored easily by both patient and physican

The Sentry 75 is powered by the industry s first mercury/zinc cells specifically designed for implantable pulse generator applications A complete redesign of both this power cell and circuitry now make possible a pulse generator which can be expected to deliver a 4 to 6 year life with an assurance factor greater than generators using normal mercury/zinc batteries

Your GE representative can provide you with information regarding patient testing warranties and availability in your area

Optimized power source capability



Redesigned power cells The mercury/zinc battery is a long proven power source familiar to the medical profession Its chief liability has not been in the chemical composition but in its construction GE design aims were to maximize power utilization and reduce internal losses to produce a power cell capable of far longer and more reliable service life

Note the new GE power cell is rectangular It displaces the same volume as 2 circular batteries yet contains 50% greater capacity (3000 mA hours vs 2000) than 2 circular batteries operating in parallel Two of these high capacity cells connected in series power the pulse generato

Internal discharge a p ob with previous batteries resulting from shorting electrodes has been virtu eliminated by 6 wraps of a non degradeable separat These multi wraps replace single wrap separator presently used in mercury zinc batteries

The power cell case is soli nickel to prevent case-to-electrolyte reaction anoth potential source of self discharge

Welded internal contacts electrodes preclude the possibility of open cont a design shortcoming with ordinary pressure contact

The negative terminal is isolated from the cap thro a hermetic ceramic to-met seal and the cap is welded the top of the cell to preven electrolyte seepage across 2 terminals And as one las safety precaution the posi pressure vent is located at end of the cell remote from the terminals

Experimental and laboratory reports

Electrophysiological evaluation of disopyramide in man

Mark E. Josephson, M.D.
Anthony R. Caracta, M.D.
Sun H. Lau, M.D.
John J. Gallagher, M.D.
Anthony N. Damato, M.D.
Staten Island, N. Y.

Disopyramide (Norpace)* is a new antiarrhythmic agent available in Europe (Rythmodan) with a reported antiarrhythmic spectrum similar to that of quinidine. It has been used orally and parenterally and has been found useful in the management of paroxysmal arrhythmias and extrasystoles of ventricular or supraventricular origin.[1-5] This study was undertaken to analyze the effects of intravenously administered disopyramide on the refractory periods (RP) of the atrium (A), A-V node (AVN), and His-Purkinje system (HPS) as well as on conduction through the AVN and HPS in man.

Methods and materials

Twelve patients underwent right heart catheterization in the nonsedated post-absorptive state after informed consent was obtained. Clinical data are listed in Table I. Five patients had arrhythmias and/or conduction disturbances while the others were studied during the course of catheterization for other reasons.

A quadripolar electrode catheter was inserted percutaneously into an antecubital vein and positioned fluoroscopically against the lateral wall of the right atrium. The two distal electrodes were used to pace the atrium while the proximal pair recorded a high right atrial (HRA) electrogram. His bundle electrograms (HBE) were obtained according to methods previously described.[6,7] Three or four surface electrocardiographic leads were simultaneously recorded (I, II, III, +/− V_1). Each patient was paced at several basic cycle lengths for 30 to 60 seconds during which time records were made of A-V nodal and His-Purkinje conduction time (*vida infra*). Refractory periods were determined by the extrastimulus method[8] using a specially built programmed digital stimulator which delivered rectangular impulses of 1.5 msec. duration at twice diastolic threshold. Progressively more premature impulses were delivered after every eighth spontaneous or paced beat until the effective refractory period (ERP) of the atrium was reached. Refractory period studies were carried out at paced atrial cycle lengths in 11 patients

From the Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y.
This work was supported in part by the Federal Health Programs Service, United States Public Health Service Project [illegible] Py 72-1, National Heart & Lung Institute Project HE 118[illegible]9 and HE 12536.
Received for publication J[illegible] 15, 1973.
Reprint requests to: Mark E. Josephson, M.D., Cardiopulmonary Laboratory, United States Public Health Service Hospital, Staten Island, N. Y. 10304.
*Kindly supplied by G. D. Searle and Co., Chicago, Ill.



Patient management

The Sentry 75 pulse generator has a built in service life indicator that is simple and easy to use The pulse generator s pacing rate is highly dependent upon battery voltage thus as battery voltage begins to fall near end of life pacing rate will decrease This change in rate can be easily and accurately monitored when a GE patient sensor and rate interval computer are used The latter is a desk top unit which used in conjunction with the patient sensor *enables* the physician to check the patient s pacemaker over the phone between regular office visits The patient can also be instructed to check his own rate with the sensor

Clinical evaluation

Laboratory tests of the Sentry 75 components were con ducted for 2 years before any implants in humans were undertaken Clinical evalua tions began on a worldwide basis in November 1972 Physicians representing more than 15 major hospitals and medical centers are participating in the program

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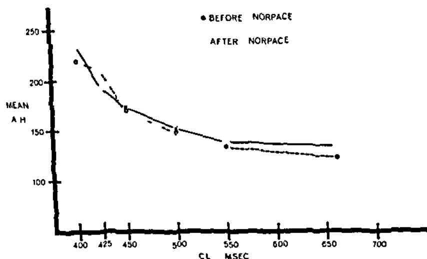


Fig 1 Thi graph demon trates the effects of di opyramide on \ V nodal conduction at different paced rates Mean A H i plotted on the ordinate and paced cycle length on the abscissa It can readily be seen that there is no gnificant difference in response after di opyramide (Norpace)

Table III *Effect of disopyramide on the ERP of the atrium**

Patient No	*Cycle length at which study done*	*ERP before Norpace*	*ERI after Norpace*
1	500	290	290
2	NSR†	340	340
3	NSR	200	260
	550	200	210
4	600	230	240
5	NSR	340	320
	860	280	280
	600	2?0	280
	500	280	270
6	600	290	280
7	850	290	280
	800	260	?75
8	NSR	2?0	260
	700	260	2?0
	600	240	270
9	750	?45	?80
	600	235	260
10	700	240	270
	= 1 mg /kg		
	600	?45	270
	700	240	265
	= 1 5 mg /kg		
	600	240	265
11	NSR	?60	260
12	NSR	310	260
	600	?55	290
	Me n ERI ± standard error of mean	256 ± 6	269 ± 4
	Net change = 13		
	P value 005		

*N 1 msec
†NSR = no mal bythm

Table I. Clinical data

Patient No	Age	Sex	Weight (kg)	Dose of disopyramide (mg)	Heart disease	Medication
1	66	M	70	140	ASHD	None
2	41	M	80	120	None	None
3	55	M	60	90	Myotonic dystrophy	None
4	52	M	60	60	ASHD	Off digoxin
5	54	M	85	135	ASHD	None
6	40	M	80	80	None	None
7	53	M	70	140	ASHD	None
8	36	M	85	85	ASHD	None
9	18	M	80	80	Myotonic dystrophy	None
10	74	M	70	70 100	ASHD	None
11	67	M	90	180	ASHD	None
12	45	M	60	90	ASHD	None

*Table II. Effects of disopyramide on A-V nodal conduction at paced rates**

Patient No	660		550		500		450		4?5		400	
	B	A	B	A	B	A	B	A	B	A	B	A
1	110	100	110	120	130	140	180	180	200	2 0	200	W
2	110	130	130	145	W	W	—	—	—	—	—	—
3	—	—	140	150	170	170	170	180	210	225	0	270
4	95	95	110	100	115	110	120	115	W	120	W	[illegible]
5	110	110	135	110	145	120	170	150	200	175	W	185
6	95	135	115	160	1 0	170	210	280	215	W	—	—
7	90	100	110	110	—	—	—	—	—	—	—	—
8	130	155	175	190	210	00	W	220	—	W	—	—
9	200	260	W†	3 0	—	W	—	—	—	—	—	—
10	175	160	180	170	205	190	215	195	245	225	W	W
11	110	90	1 0	105	1 0	105	140	115	235	125	W	245
12	—	—	—	—	145	165	—	—	170	185	2 0	200
Mean A-H ± SEM	123 ± 12	134 ± 16	133 ± 8	136 ± 10	151 ± 12	152 ± 12	172 ± 13	174 ± 21	174 ± 21	210 ± 16	20 ± 0	235 ± 35
Net change	+ 11		+ 3		+ 1		+ 2		− 17		+ 15	
% change	9%		2.3%		− .7%		1.0%		8.1%		6.7%	
P value	.2		> .5		> .5		> .5		> .5		> .5	

*Values are expressed in msec.
†W = Wenckebach.

to avoid the effect of changing cycle length on refractoriness. In 7 patients refractory periods were also studied during normal sinus rhythm.

After control values were obtained, each patient was given 1 to 2 mg. per kilogram of body weight of disopyramide intravenously over a 5 to 10 minute period. One patient (No. 10) was studied at two dose levels. Studies of conduction and refractory periods were then repeated. Blood pressure was frequently measured throughout the study with a sphygmomanometer. Careful attention was paid to note any clinical signs of myocardial depression.

Time lines were generated at 10 and 100

Table IV Effects of disopyramide on the ERP of the AVN*

Patient No	CL§	B	I
1	500	330	360
2	NSR§	350	340
	700	450	400
4	NSR	300	260
	600	370	270
5	500	310	270
6	600	380	280
8	NSR	330	375
	700	370	360
	600	410	390
9	750	385	390
	600	460	450
10	700 }†	330	330
	600 }†	350	350
	700 }‡	330	330
	600 }‡	350	340
12	600	295	295
	Mean ± SEM	366 ± 13	344 ± 14
	Net change	−22	
	P value	05	

*Val [illegible] msec.
† [illegible]0 mg disopyramide.
‡[illegible]00 mg disopyramide
§Abbreviations CL = cycle length NSR = normal [illegible] rhythm.

longest $H_1 H_2$ interval at which H_2 fails to depolarize the ventricles

The relative refractory period (RRP) of the HIS is defined as the longest $H_1 H_2$ interval at which H_2 conducts to the ventricles with a longer H V interval than that of the basic drive beat or with a QRS of aberrant configuration This definition presupposes that the HPS functions as a single unit Although it is recognized that the HPS is a trifascicular system in the absence of multiple recording sites along individual fascicles it is impossible to precisely measure the ERP versus the RRP of any given fascicle Thus for the purposes of this study it was elected to consider the HPS as a single functioning unit and the RRP as so defined

Results

Spontaneous sinus cycle length was unchanged or insignificantly (< 100 msec) decreased in 9 patients but in 3 patients (Nos 3 4 and 5) it was shortened by 120 to 160 msec

A V nodal conduction Disopyramide variably and insignificantly affected A V nodal conduction during sinus rhythm increasing it in five decreasing it in two and not changing it in the remaining five patients Table II summarizes the effects of disopyramide on A V nodal conduction as measured by A H interval at several paced rates At any paced atrial rate A V nodal conduction was not significantly altered by disopyramide (Fig 1) However it should be noted that in 5 patients (Nos 4 5 8 9 and 11) A V nodal Wenckebach occurred at higher paced rates than during control A sixth patient (No 10) showed enhancement of A V nodal conduction although Wenckebach developed at the same paced rate as it did during control studies Thus several patients showed enhancement of A V nodal conduction during atrial pacing compared to control

His Purkinje conduction Control H V values were normal in 9 patients (35 to 55 msec) and abnormal in 3 (Nos 3 9 12— 60 to 62 msec) In 10 of 12 patients

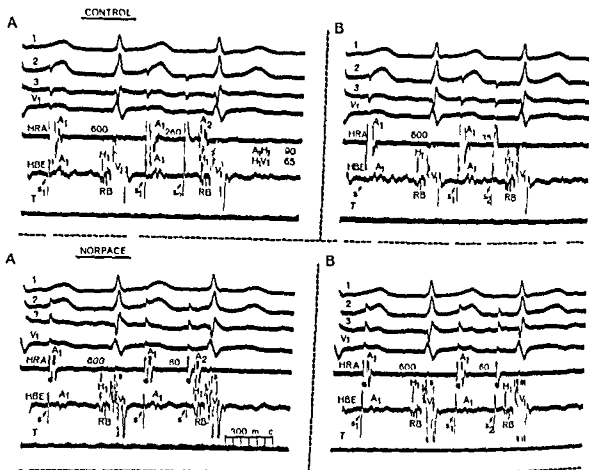


Fig. 2. A and B. Effects of disopyramide (Norpace) on the ERP of the atrium. Panels A and B in the *control* and *after disopyramide* represent the shortest A_1A_2 (*panel A*) and S_1S_2 at which S_2 fails to capture the atrium—i.e., ERP of the atrium (*panel B*). In this patient at a paced cycle length of 600 msec. the ERP of the atrium is increased 25 msec. (235 to 260 msec.) after disopyramide.

msec. All data were stored on magnetic tape* and later retrieved at paper speeds of 150 mm. per second.†

A thirteenth patient, not listed in Table I, who did not undergo cardiac catheterization was given a 2 mg. per kilogram of body weight bolus of disopyramide during an episode of supraventricular tachycardia and electrocardiographic changes were recorded.

Statistical data were calculated using the Student t test for paired data. In evaluation of refractory periods statistical analysis was only applied to those determinations obtained during paced atrial cycle lengths. This eliminates the effects of changing cycle length or refractoriness.

*North American Phillips, Shelton, Conn.
†Electronics for Medicine, White Plains, N. Y.

Definition of terms

The A-H (atrium to His) interval as measured in the His bundle electrogram recording was taken as a measure of A-V nodal conduction time (nl 60 to 140 msec.).

The H-V (His to ventricle) interval was taken as a measure of His-Purkinje conduction time (nl 30 to 55 msec.).

The effective refractory period (ERP) of the atrium is defined as the longest S_1S_2 that does not result in atrial depolarization.

The ERP of the AVN is defined as the longest A_1A_2 interval at which A_2 depolarizes the atrium but does not propagate to the HPS.

The functional refractory period (FRP) of the AVN is defined as the shortest H_1H_2 interval resulting from any two consecutive propagated atrial depolarizations.

The ERP of the HPS is defined as the

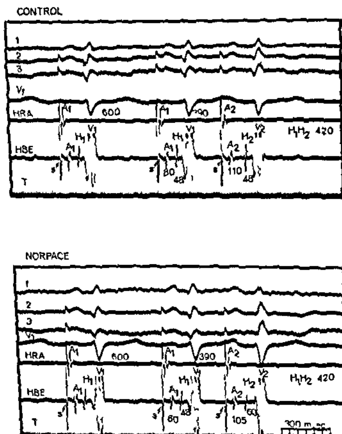


Fig 4 Effect of disopyramide (Norpace) on the RRP of the HPS This patient while being paced at a cycle length of 600 msec showed no aberration or HV prolongation at an H_1H_2 of 420 msec before disopyramide After disopyramide at the same H_1H_2 of 420 msec the HV is prolonged to 60 msec and aberration in the form of incomplete LBBB is present Thus in this patient the RRP of the HPS was prolonged by disopyramide

mined since right heart catheterization was not performed In this patient disopyramide slowed the ventricular response from 1 0 to 120 (Fig 5) Continued oral disopyramide 100 mg Q I D for two days converted the arrhythmia to sinus rhythm

Side effects The only side effect noted was dry mouth present in two patients There was no significant hypotension myocardial depression or conduction disturbances noted

Discussion

Disopyramide is a new antiarrhythmic agent which shares many clinical properties with quinidine even though its chemical structure is very different It has received many trials in Europe and apparently has its major use in the treatment of supraventricular and ventricular extrasystoles and in the prophylaxis of paroxysmal arrhythmias[1-6] There are conflicting data on its usefulness in chronic atrial fibrillation[5] A few studies have shown it to be effective in the prevention of arrhythmias after acute myocardial infarction[6] It may be given orally in doses of 100 to 200 mg q i d or may be given intravenously at a dose of 1 to 2 mg per kilogram of body weight Its action is relatively rapid when given intravenously

Little is known about the electrophysiological properties of disopyramide in man Several studies[11-13] in dogs found dose related increases of the A V functional RP and A V conduction time There is also some evidence that disopyramide may slow His Purkinje conduction and diminish

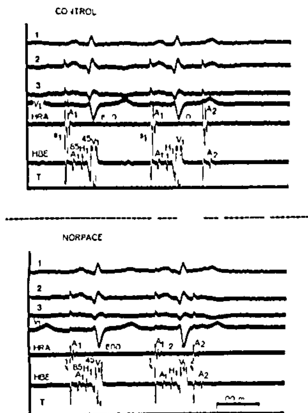


Fig. 3. Effects of disopyramide (Norpace) on the ERP of the AVN. This patient while being paced at a cycle length of 600 msec reached the ERP of the AVN at an A_1-A_2 of 370 msec during control studies. After disopyramide block in the node first appears at an A_1-A_2 of 270 msec. Thus the ERP of the AVN was shortened 100 msec.

disopyramide had no effect on H-V intervals at sinus rhythm or at various paced atrial rates. In two patients (Nos. 3 and 5) the H-V interval increased by 5 and 10 msec (50 to 55 and 60 to 70 msec.) after 1.5 mg. per kilogram of body weight of disopyramide.

Refractory studies. Although refractory periods were determined at sinus rhythm as well as during paced rates in most patients, only those values obtained during paced cycle lengths were considered valid due to the known effects of changing cycle lengths on refractoriness. Therefore all calculations of mean and P values were derived from the results of only those studies done at paced cycle lengths.

ERP of the atrium. Table III summarizes the effects of disopyramide on the ERP of the atrium. The ERP of the atrium was increased by 13 msec. This is a small but statistically significant change (p = .005).

In only three patients did the ERP decrease after disopyramide. Fig. 2 is from patient No. 9 in whom disopyramide lengthened the ERP of the atrium from 235 to 260 msec.

ERP of the AVN. The ERP of the AVN could be measured in only nine patients. In the remaining 3 patients the ERP of the atrium was reached before that of the AVN. The results are summarized in Table IV. On the average the ERP of the AVN was shortened 22 msec. after disopyramide. This is significant to a P value of .05. Fig. 3 demonstrates a 100 msec. shortening of the ERP of the AVN after disopyramide.

FRP of the AVN. The FRP of the AVN was not significantly changed by disopyramide in spite of the fact that the ERP of the AVN was shortened.

ERP and RRP of the HPS. No patient developed block within the HPS during paced rates; therefore no comment can be made on disopyramide's effect on this parameter. One patient did develop block in the HPS during NSR and in this patient disopyramide shortened the ERP by 20 msec. The meaning of this is not clear since this patient had changing atrial cycle lengths at NSR both before and after disopyramide, and this may have altered the refractoriness of the HPS.

Disopyramide prolonged the RRP of the HPS in two patients. In one patient the RRP increased by 20 msec. at two paced rates after disopyramide. In the other patient incomplete LBBB developed after disopyramide where no aberration was present prior to its administration. This is shown in Fig. 4.

Runs of supraventricular tachyarrhythmias were noted in two patients (Nos. 12, 13). One patient (No. 12) developed repeated episodes of A-V nodal re-entrant type paroxysmal atrial tachycardia (PAT) in response to electrically induced atrial depolarizations. In this patient disopyramide shortened the critical A-V nodal delay required to produce PAT from 190 to 175 msec. However, the R-R interval of the re-entrant rhythm was unchanged. The second patient (No. 13) spontaneously developed a supraventricular tachycardia, the mechanism of which could not be deter-

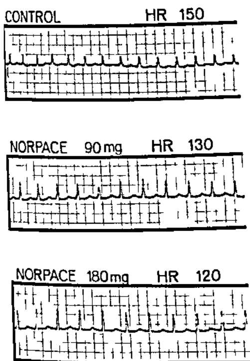


Fig 5 Effect of disopyramide (Norpace) on supraventricular tachycardia This patient developed a supraventricular tachycardia with a ventricular response of 150 beats per minute After 180 mg of disopyramide the ventricular rate had gradually decreased to 120 beats per minute No discrete P waves are seen

nodal refractoriness Alternatively since none of the studies in dogs utilized His bundle electrograms the site of increased refractoriness could not be accurately determined Our studies demonstrated that in the small number of cases where it could be measured the RRP of the HPS was increased thus the reported increase in atrioventricular refractoriness may have been related to disopyramide s effect on the HPS not the AVN This effect of shortening the ERP of the AVN may have clinical relevance since an increase in ventricular response during treatment of atrial flutter and fibrillation has been seen [4,5]

Although we did not correlate electrophysiological effects of disopyramide with plasma levels the doses used are considered therapeutic [5] Oral doses as low as 100 mg per day have been effective in the treatment of arrhythmias [3] Intravenously administered disopyramide has a relatively rapid onset of action and a half life of 1 4 to 2 hours [12] Since our studies took approximately 30 minutes we felt therapeutic levels of disopyramide were present In no case was the severe myocardial depression[19] and hypotension[19] seen in dogs noted

Conclusion

The results presented above suggest that disopyramide

(1) has no significant effect on sinus automaticity
(2) has no significant effect on conduction through the AVN or HPS
(3) produces a small but probably clinically insignificant increase in the ERP of the atrium
(4) shortens the ERP of the AVN without significantly affecting the FRP of the AVN
(5) prolongs the RRP of the HPS
(6) has no significant side effects at the doses used in the present study
(7) has an unclear mechanism of antiarrhythmic action

The author wish to acknowledge the assistance of Audrey Pedersen Mary Vecchione Michael Moretti Anne Mazzella and Kenneth Donohue

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*Table V Effect of disopyramide on the ERP of the AVN**

Patient No	CL†	Before	After
1	500	430	450
2	NSR	490	440
	700	560	480
3	NSR	380	400
	550	360	380
4	NSR	390	415
	600	420	360
5	NSR	430	410
	860	400	420
6	600	495	495
7	850	420	435
	800	415	430
8	NSR	450	465
	700	470	475
	600	470	480
9	750	560	550
	600	550	510
10	400	445	445
	600	435	435
	700	445	430
	600	435	425
11	NSR	410	405
12	NSR	440	430
	600	415	430
	Mean ± SEM	447 ± 14	442 ± 11
	Net change	−5	
	P value	> 5	

*Values in msec
†Abbreviations CL = cycle length NSR = normal sinus rhythm

phase 4 depolarization of the HPS in dogs[5] These studies all used doses that were above what is considered therapeutically safe in man Studies in man have shown variable ECG changes including prolonged PR and QT interval widened QRS T and U wave changes in 5 to 25 per cent of cases[1 6] None of these previous reports separated the effects of disopyramide on the AVN and HPS Using the present methods it has been possible to determine the electrophysiological properties of drugs in man[14 15] The results of this study reveal that disopyramide caused no significant change in A V nodal conduction time during sinus rhythm or at paced rates up to 150 Only two patients show an increase in His Purkinje conduction time which was minimal (5 and 10 msec) and two patients (Nos 9 and 12) whose control H V intervals were already prolonged had no further depression of His Purkinje conduction Thus, unlike procainamide[16 17] and quinidine[14 18] which depress AVN and HP conduction disopyramide does not and might therefore be indicated in the treatment of arrhythmias which are associated with some degree of atrioventricular block

Our study confirms data from studies in dogs that the ERP of the atrium was increased Although our result was statistically highly significant (p = 005) the increase of 13 msec is probably not of clinical significance This might explain its variable success in the conversion of atrial fibrillation to NSR

The fact that disopyramide shortened the ERP of the AVN in man came as a surprise in view of all animal work which showed a dose related increase in A V nodal refractoriness[4 11 14] There are two possible explanations for this discrepancy Disopyramide has anticholinergic properties[4] which may have caused a decrease in A V

Are patients with essential hypertension and low renin protected against stroke and heart attack?

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Brunner and colleagues[1] reported recently on 219 patients with essential non malignant hypertension without heart failure Their plasma renin activity was related to daily sodium excretion and compared to a normogram from 52 normal volunteers studied over the same continuous range of sodium balance On the basis of this plasma renin level patients were divided in three groups patients with abnormally low plasma renin level (27 per cent) patients with normal plasma renin level (57 per cent) and patients with abnormally high plasma renin level (16 per cent) Compared to the first two groups the high renin group had higher diastolic blood pressure and more cardiovascular complications of high blood pressure (14 per cent) Apart from the renin level the groups with low and normal renin level did not differ from each other according to other known risk factors for cardiovascular disease including diastolic blood pressure Nevertheless strokes and heart attacks were not noted in the low renin group and were present in 11 per cent of the patients with normal renin levels The authors conclude that plasma renin activity emerges as a potential risk factor for patients with essential hypertension and even suggest that those antihypertensive agents that can correct renin abnormalities could produce a more satisfactory blood pressure response

The purpose of the present paper is first to present the results of an analysis of these criteria in our patients with essential hypertension in an attempt to test the Laragh hypothesis and second to comment on both studies

Selection of patients

The last 59 patients hospitalized in our department and discharged with the final diagnosis of essential hypertension were included in this retrospective study irrespective of severity and complications of hypertension

Methodology

Blood for renin determinations was withdrawn in basal conditions i e after at least four weeks interruption of diuretics antihypertensive agents and oral cont

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Table III Biochemical data in patients with essential hypertension divided into three groups according to the plasma renin concentration

	Low renin	*Middle renin*	*High renin*
Total number of patients	20	19	20
Plasma renin concentration range	1 8 – 6 5	8 – 13 4	14 – 49
(Skinner[2] U/ml) (x̄ ± S D)	4 5 ± 1 5	10 5 ± 1 9	22 3 ± 8 5
Plasma cholesterol (x̄ ± S D) (mg %)	238 ± 40	225 ± 37	254 ± 56
Plasma lipid (x̄ ± S D) (mg %)	630 ± 161	511 ± 113	643 ± 117
Serum creatinine (x̄ ± S D) (mg %)	1 21 ± 0 4	1 15 ± 0 4	1 14 ± 0 3
Creatinine clearance (x̄ ± S D) (ml /min)	79 ± 28	83 ± 22	93 ± 29

Table IV Some cardiovascular complications in patients with essential hypertension divided into three groups according to the plasma renin concentration

	Low renin	*Middle renin*	*High renin*
Number of patients at risk	20	19	20
Patients with heart failure	2	1	1†
Patients with stroke	1	2	1†
Patients with heart attack	1	1	3†

*One patient had both heart failure and heart attack
†One patient had all three complications

using the method of Skinner[2] with minor modifications With this method normal values range from 8 to 25 units per ml On the basis of the renin determinations the 59 patients were divided in three tertiles containing 20 or 19 patients each the three groups thus constituted were compared with each other

Other analysis of serum plasma or urine were made with the standard Auto Analyzer technique except for urinary sodium which was measured by internal standard flame photometry

The blood pressure was measured at the time of blood sampling for renin using a standard sphygmomanometer and taking Phase 5 as diastolic blood pressure

Results

According to the described techniques one third of the patients (n = 20) had a basal plasma renin concentration below 7 units per ml the plasma renin level of the middle tertile (19 patients) ranged from 7 to 13 9 the renin level of the upper tertile (n = 20) was 14 units or above

Before studying the incidence of stroke and heart attack in these three groups we analyzed first if the three groups were comparable concerning other known risk factors for cerebrovascular and coronary heart disease As shown in Tables I II and III no significant differences were found between the three groups in the incidence of the different mentioned factors

Table IV and Fig 1 show the incidence of stroke heart failure and heart attack in these three groups No significant differences were found

In the study of Brunner and colleagues[1] patients with heart failure and malignant hypertension were not entered If we withdraw the patients with heart failure from our study we retain one patient with stroke and one patient with heart attack

Table I. Data from history in patients with essential hypertension divided into 3 groups according to the plasma renin concentration

	Low renin	Middle renin	High renin
Total number of patients	20	19	20
Sex			
Male	11	10	6
Female	9	9	14
Age ($\bar{x} \pm$ S.D.) yr	46.2 ± 15.3	45.3 ± 10.6	46.7 ± 14.5
Number with positive family history for stroke, hypertension or heart attack	14	9	15
Number of smoking			
No cigarettes	11	7	14
Less then 10 cigarettes a day	2	3	2
10 or more cigarettes a day	7	8	4
Unknown	0	1	0
Known duration of hypertension ($\bar{x} \pm$ S.D.) yr	4.7 ± 5.9	7.4 ± 1.9	10.0 ± 8.6

Table II. Physical examination in patients with essential hypertension divided into three groups according to the plasma renin concentration

	Low renin	Middle renin	High renin
Total number of patients	20	19	20
Height ($\bar{x} \pm$ S.D.) (M.)	1.64 ± 0.1	1.67 ± 0.1	1.61 ± 0.1
Weight ($\bar{x} \pm$ S.D.) (Kg.)	69.3 ± 10.1	75.0 ± 14	71.7 ± 14
Systolic blood pressure ($\bar{x} \pm$ S.D.) (mm. Hg)	179 ± 29	182 ± 22	184 ± 21
Diastolic blood pressure ($\bar{x} \pm$ S.D.) (mm. Hg)	120 ± 28	117 ± 14	113 ± 13
Number with hypertensive retinopathy according to Keith Wagener			
State I	8	11	9
Stage II	9	5	7
Stage III	3	3	3
Stage IV	0	0	1
Number with left ventricle hypertrophy on E.C.G.	9	7	8
Number in WHO classification			
Stage I	10	11	7
Stage II	5	3	6
Stage III	5	5	6
Stage IV	0	0	1

ceptives fasting in the morning recumbent, before rising after three to seven days admission to the hospital while on a daily sodium intake of 100 to 200 mEq. The urinary sodium excretion was measured during the 24 hours prior to this blood sampling and ranged in fact from 87 to 204 mEq. with an average of 134 mEq. Ten ml. blood were withdrawn in an ice cooled tube containing 0.2 ml. Na-ethylenediaminetetraacetic acid (60 mg./ml. solution) and centrifuged at 4° C. The plasma was deep frozen at −20° C. the renin concentration _ determined

attack are too small to substantiate or invalidate the Laragh hypothesis Lacking a valid control series we classified our patients in three tertiles and compared the three groups

Although our series is small two patients with non malignant essential hypertension without heart failure and with low renin developed complications (stroke and heart attack) According to the suggestion of Brunner and colleagues[1] these patients should have been protected by their low renin

III Comparison between the low renin groups of both series In view of these divergent results we wonder what is the difference between the study of Brunner and colleagues[1] and the present study?

A The selection was different In our study only white patients and patients with essential hypertension were initially admitted and patients with heart failure or malignant hypertension were also included however as discussed above exclusion of the latter patients would not basically influence the results

B Our patients with low plasma renin concentration had probably more severe hypertension indeed while the diastolic blood pressure in our low renin group averaged 120 mm Hg the diastolic blood pressure in Brunner and colleagues[1] low renin group averaged 105 mm Hg

Furthermore the average creatinine clearance of the low renin group in our study was 79 ml per minute while in the study of Brunner and colleagues[1] it was 95 ml per minute

The degree of retinopathy could not be compared since no exact figures were given in the paper of Brunner and colleagues[1] Left ventricular hypertrophy was present in 20 per cent of Brunner s and in 45 per cent of our low renin patients Although the criteria for left ventricular hypertrophy may have been different the greater percentage in our study is in accord with the higher diastolic pressure and lower creatinine clearance The larger number of patients with more severe hypertension in our low renin group could explain the higher incidence of cardiovascular complications when compared with Brunner and colleagues[1] low renin group

Based on Brunner and colleagues[1] communication one could speculate that a low renin level might protect against stroke and heart attack only if the hypertension was moderate but this of course remains to be confirmed

C Differences in methodology have also to be considered Brunner and colleagues[1] measured plasma renin activity while the method used in our study (Skinner[7]) is thought to measure plasma renin concentration Brunner and colleagues[1] drew blood at noon after their patients had been ambulatory for at least 4 hours while we drew blood in the morning our patients having been recumbent overnight Furthermore the mean urinary sodium excretion in Brunner and colleagues[1] low renin group was 16 1 mEq per 24 hours while the 24 hour urinary sodium excretion in our own study ranged between 87 and 204 mEq It is not clear to us how these differences in methodology could explain the differences in cardiovascular complications

D The general approach in both studies was different Brunner and colleagues[1] compared the plasma renin levels of their patients with those of normal volunteers while we classified our patients in three tertiles according to their plasma renin concentration

We have already discussed the fact that Brunner and colleagues[1] control series did not contain any black subject but this would not invalidate their results if we consider only their patients and exclude their control group

We then find in Brunner and colleagues[1] low renin group 27 per cent of their patients which is similar to 1/3 or 33 per cent of patients in our low renin group

This difference in the classification system would not change our patients with stroke and heart attack from the low to the middle renin group since their plasma renin concentration was indeed very low as indicated in Fig 1 namely 3 and 3 8 units per ml respectively

IV General conclusion and prospectives In conclusion in our study we did not find any data to confirm the hypothesis of Brunner and colleagues[1] concerning the protection against stroke and heart attack by a low plasma renin level It is possible that

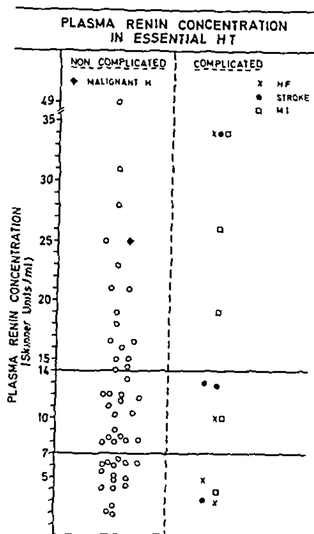


Fig. 1. Plasma renin concentration in essential hypertension. Each sign represents the plasma renin concentration of the respective 59 patients with essential hypertension. The patients represented in the right column under the heading *COMPLICATED* had at least one of the three following complications: heart failure (x), stroke (●), or myocardial infarction (□); the patient with two and the other with three complications at the same time are represented by two or three signs surrounded by a dotted line. The patients without any of these three complications are represented in the left column under the heading *NON COMPLICATED*; they include patients with benign essential hypertension (○) except for one who had malignant hypertension (⊕). The two horizontal lines represent the dividing lines between the three groups of patients and not the limits of the normal range.

in the low renin group; we also retain in these circumstances two patients with stroke in the middle renin group and two patients with heart attack in the high renin group. In our study only one patient with malignant hypertension (defined by the presence of a high blood pressure and papilledema) was entered. As can be seen from Fig. 1, he had a high plasma renin concentration and no heart failure, heart attack, or stroke. Withdrawing this one patient would therefore not influence the incidence of cardiac complications or stroke in any group.

Discussion

I. Discussion of the paper of Brunner and colleagues.[1] The study of Brunner and colleagues[1] performed in well standardized conditions of sodium intake in a large group of hypertensive patients with a big control series yielded provocative results and led to a discussion in the medical literature during the past year—an editorial in the *British Medical Journal*,[5] the *Lancet*,[6] and a letter by Golby and associates[7] and Schalekamp and co-workers.[8] We will review these comments and add some more remarks.

A. Brunner and colleagues[1] mentioned that there was no significant difference in the average diastolic blood pressure (DBP) between the group with low (DBP = 105 ± 14 mm. Hg) and normal renin (DBP = 104 ± 17 mm. Hg). They did not discuss, however, the variability of the blood pressure. Also, the systolic blood pressure in itself could be considered as a risk factor.

B. It is generally accepted that for the same blood pressure duration females have less cardiovascular complications than males. The authors did not mention in their paper the sex ratio in the three groups.*

C. The percentage of black patients in the low renin group (42 per cent) was higher than in the normal renin group (24 per cent); furthermore, the percentage of black subjects in the control group was not mentioned. Therefore we do not know if the control and the patient series are matched for this criterium.†

II. Discussion of the present paper. The present study lacks the numbers and comparison with a control series when compared with the study of Brunner and colleagues.[1] Indeed, in our study the numbers of patients with stroke or heart

*According to a recent personal communication from Laragh the sex ratio was the same in the three groups.
†According to a personal communication from Laragh the control group did not contain any black subject.

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the higher complication rate in our low renin group could be related to the more severe hypertension in our group

A prospective study of this topic is needed to investigate several problems raised by these previous studies, but not yet clearly solved

(1) Should we consider these three groups as three distinct entities as suggested by Brunner and colleagues[1] or as three stages in the evolution of hypertension in the single patient as suggested by Schalekamp and associates[8] The impression of Brunner and colleagues[1] was that the patients did not change from group to group, although their follow up was too short to enable definite conclusions

(2) Furthermore the possibility should be excluded that a stroke or myocardial infarction may cause an increased plasma renin level the increase in renin therefore being the consequence rather than the cause of the cardiovascular complication

(3) Because both studies were retrospective the influence of previous treatment could not be evaluated It is indeed possible that previous antihypertensive treatment could have prevented cerebrovascular accidents in the low renin group although it is not clear if this treatment could also prevent heart attacks

(4) In an editorial Laragh[3] suggested that antihypertensive agents which lower plasma renin levels (e g beta blocking agents methyldopa clonidine, reserpine) should be preferred to those which increase the renin levels (e g diuretics) He did not present a direct proof of this statement It should be remembered however that although the influence of short term treatment of several antihypertensive agents on plasma renin levels is well known the influence on circulating renin of long term treatment with these drugs is often debated, because of conflicting results

Furthermore, diuretics which are known to increase plasma renin levels at least in acute experiments, have been used in combination with other antihypertensive agents in several studies which have shown a decreased incidence of strokes It is unlikely that the beneficial effect of this combined treatment was related exclusively to the non diuretic agents In a more recent article Laragh and colleagues[4] mentioned the possibility that the vasculotoxicity supposedly due to increased renin levels, which could be suspected to be present during thiazide treatment, might be prevented by the diuretic action of these drugs themselves

As long as these problems have not been adequately solved in prospective studies therapeutic conclusions drawn from these data could be premature

Summary

Fifty nine patients with essential hypertension were divided into three tertiles based on their plasma renin concentration determined on blood withdrawn in standardized conditions of day physical activity sodium intake and drug treatment

The incidence of known risk factors for cardiovascular disease such as sex age family history cigarette smoking obesity systolic and diastolic blood pressure plasma cholesterol and lipids did not differ significantly between the 20 patients with low renin levels (below 7 Skinner units per milliliter) the 19 patients with middle range renin levels (between 7 and 14 U per milliliter) and the 20 patients with high plasma renin levels (14 units per milliliter or more)

The incidence of stroke and heart attack was the same in the three groups irrespective of whether patients with heart failure and with malignant hypertension were included or excluded from the series

We therefore could not find from our data a support for the hypothesis which suggests that low renin protects hypertensive patients against stroke and heart attack The differences between this study and the study of Brunner and associates[1] and Laragh and colleagues[4] are discussed in an attempt to explain this divergent tendency It is felt that therapeutic conditions cannot be drawn from this small and retrospective study but that large scale prospective studies are needed

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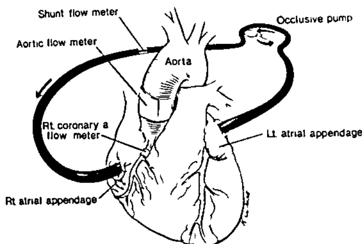


Fig 1 Diagram showing experimental preparation Right ventricular output increased by shunting blood from the left atrium to the right atrium through external conduit Left ventricular output and shunt flow were monitored with electromagnetic flowmeters

Methods

We anesthetized 9 dogs weighing 16 to 28 kilograms with sodium pentobarbital 30 mg per kilogram of body weight intravenously and gave supplemental amounts when needed The dogs were ventilated by a Harvard respirator through an endotrachial tube with oxygen enriched gas mixtures to give arterial oxygen tensions greater than 100 mm Hg and carbon dioxide tensions between 28 to 40 mm Hg A bilateral thoracotomy was done through the fourth intercostal space Catheters were placed in both femoral arteries a femoral vein the ascending aorta left atrium distal pulmonary artery and directly into the right ventricle through the outflow tract Pressures were measured with Statham P 23Db transducers and recorded by a Beckman oscillograph A tourniquet of umbilical tape placed around the main pulmonary artery could be tightened to produce the desired level of right ventricular hypertension

Number 34F Bardex tubes were inserted through the left and right atrial appendages (Fig 1) A 10 mm internal diameter (I D) cannulating electromagnetic flow transducer (Statham Model SP 2202) was placed in the tubing connecting the two atrial cannulae and the tubing was inserted into an occlusive roller pump to control the size of the interatrial left to right shunt Aortic flow was recorded with 13 to 16 mm I D electromagnetic flow transducers (Statham) placed around the ascending aorta and pulmonary flow was calculated as the sum of aortic and shunt flows The flow transducers were calibrated *in vitro* with timed volume collections of blood A 2 0 mm I D electromagnetic flow transducer (Statham) was placed around the proximal right coronary artery to measure changes in the post occlusive hyperemic response [4] Zero flow reference levels were determined by 8 second occlusions of the right coronary artery distal to the flow transducer The flow debt during occlusion was calculated as baseline flow times the duration of occlusion The payback of this debt was calculated by planimetry of the area beneath the mean coronary flow curve and above the baseline flow level from the time of release of the occlusion until mean flow stabilized at or near the pre occlusive level The ratio of this payback area to the flow debt was multiplied by 100 to give the per cent hyperemic response 100 per cent indicates that the flow debt was exactly repaid [4]

We measured regional myocardial blood flow by injecting differently labeled batches of radioactive microspheres into the left atrium as described previously [5,6] Filtered microspheres with a mean diameter of 7 microns (range 4 to 12) labeled with ^{141}Ce ^{85}Sr and ^{46}Sc were used to measure intraventricular regional flow However we also used 15 micron diameter microspheres

Regional coronary flow with increased right ventricular output in anesthetized dogs

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In many types of congenital heart disease, intracardiac left-to-right shunts increase right ventricular output and frequently produce right ventricular dilatation and pulmonary hypertension. While the clinical effects of these shunts are well known, their effect on right ventricular coronary flow has not been studied. Ventricular dilatation and elevated ventricular pressure produce an increase in wall tension, hence a greater myocardial oxygen need. Whether these changes in myocardial oxygen need are accompanied by appropriate increases in right ventricular myocardial flow is not known.

Myocardial flow is determined by two main factors: coronary vascular resistance and coronary driving pressure, the latter for the right ventricle being defined as the difference between aortic and right ventricular pressures.[1] This means that with pulmonary hypertension, the increased right ventricular pressure tends to lower the coronary driving pressure. As right ventricular coronary driving pressure falls, coronary vasodilatation must occur to maintain right ventricular coronary flow. Recent studies of the right ventricle have indeed shown that the initial response to acutely increased right ventricular pressure is local vasodilatation.[2,3] Following maximal coronary vasodilatation, a further rise in right ventricular pressure lowers right ventricular coronary driving pressure and limits coronary flow. Therefore, in left-to-right shunts, right ventricular coronary flow would be adequate if there is coronary vasodilatation as right ventricular hypertension develops, but would be inadequate if maximal coronary vasodilatation occurred while right ventricular coronary driving pressure was still decreasing. The purpose of this study was to determine the effects of acute short-term increases in right ventricular output on coronary flow to the right ventricle.

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Table II Mean coronary flow values for the right and left ventricles

	Control	*Small shunt*	*Moderate shunt*	*Large shunt*	*Small shunt and RV hypertension*
REGIONAL MYOCARDIAL FLOW (ml/min 100 Gm.)					
Right ventricular					
Free wall	40 8 ± 15 8	8.8 ± .8.8†	64.5 ± 21.0†	94.2 ± 24.2†	81.8 ± 33 4†
Septal	9 2 ± 28 0	77.2 ± 36.5†	64 0 ± 15.5†	97 2 ± 28 4†	94.3 ± 16 3†
Left ventricular					
Free wall	64 0 ± 22	81 7 ± 32.3	58.5 ± 8 4	69.8 ± 22.0	69.3 ± 6 6
Septal	87 ± 23.3	84 0 ± 36 0	63.5 ± 12.1	84.5 ± 18 2	68.3 ± 28 0
MYOCARDIAL FLOW DISTRIBUTION					
Right ventricular (Free wall)					
Subendocardial / Subepicardial	78 ± 04‡	7? ± 08	0 ± 16	.63 ± .20	.69 ± 23
Left ventricular (Free wall)					
Subendocardial / Subepicardial	96 ± 10‡	90 ± 14	95 ± .29	.68 ± 09	94 ± ?1

Val ar m = one standard d iat o Co trol alues are erag f om all a mals h t alu ar not erages of the same nimals in ach g oup the ef chang flow ar m e clear-cut in Fig 1

†P < 0 05 (Diff nce f m o t l)

‡C t ol distr b ti n using 7 micro d am t microsphe es f m Ref 2

measured by planimetry of the area beneath the systolic portion of the right ventricular pressure tracings The left ventricular tension time index was measured by planimetry of the area beneath the systolic portion of the aortic pressure tracing as described by Sarnoff and colleagues [8] These indices are expressed as mm Hg sec/min that is in terms of total area per minute All statistical comparisons were made by paired t testing and by analysis of variance [9]

Results

The most prominent changes that occurred with large left to right shunts were an increase in right ventricular systolic and diastolic pressures an increase in right ventricular output and a fall in heart rate (Table I) The changes in right ventricular systolic pressure with pulmonary arterial constriction and with moderate and large left to right shunts were not statistically different from each other Left ventricular output aortic pressure and left ventricular tension time index did not significantly differ between altered states Heart rate was significantly lower than control in all except the large shunt group but did not differ significantly among the altered states

Mean coronary flow values (ml/min 100 Gm) for the right and left ventricles are listed in Table II Moderate variability in coronary flows is seen within each group even in the controls due to small differences in hemodynamics and oxygen contents It is also important to point out that the flow values in Table II are not averages of the same animals in each of the five groups since only four flow determinations could be made in any one animal Therefore changes in coronary flows are illustrated more clearly in Fig 2 where changes were analyzed with each animal serving as its own control (paired t testing) Coronary flow to the right ventricular free wall and to the right side of the septum increased initially ($p < 0.05$) with small and more with moderate left to right shunts Coronary flow failed to increase progressively however with either large or small shunts having right ventricular hypertension (right ven

Table I Findings at time of myocardial flow determinations

	Control	*Small shunts*	*Moderate shunts*	*Large shunts*	*Small shunts and RV hypertension*
Number of determinations	9	7	6	4	6
Heart rate (beats/min)	150 ± [illegible]0.3*	1[illegible]1 ± 27.2†	110.3 ± 28.1†	1[illegible]7.5 ± 8.5	1[illegible]4 ± 31.[illegible]†
Right ventricular output (L/min)	1.42 ± 0.36	3.07 ± 0.70†	3.87 ± 0.80†	5.72 ± 0.9[illegible]†	3.38 ± 0.[illegible]6†
Left ventricular output (L/min)	1.42 ± 0.36	1.60 ± 0.46	1.62 ± 0.46	2.10 ± 0.[illegible]6†	1.55 ± 0.35
Right ventricular systolic pressure (mm Hg)	[illegible]7.0 ± 6.87	37.7 ± 2.67†	37.7 ± 9.32†	45.0 ± 7.55†	54.7 ± 9.6[illegible]†
Right ventricular diastolic pressure (mm Hg)	6.7 ± 1.88	10.0 ± 0.93†	10.7 ± 3.14†	11.8 ± 1.45†	13.7 ± 3.94†
Right ventricular tension time index (mm Hg/min)	606 ± 175	950 ± 174†	1 0[illegible]0 ± 27[illegible]†	1 030 ± 353†	1 550 ± 341†
Aortic mean pressure (mm Hg)	85.2 ± 11.0	76.7 ± 26.1	78.8 ± 11.0	[illegible]8.8 ± 15.[illegible]	[illegible]7.0 ± 20.8

*Values are means ± one standard deviation
†P < 0.05 (Significant difference from control)

labeled with ^{125}I to measure interventricular myocardial flows A small Holter pump was used to withdraw reference blood samples (timed volume collections) from the femoral arteries Since well mixed microspheres are distributed to organs or regions in proportion to regional flow regional myocardial flow was determined from the equation myocardial flow/myocardial nuclide activity equals reference sample flow/reference sample nuclide activity At the end of each experiment the dog was killed and the heart was removed The atria valves great arteries large coronary vessels and epicardial fat were removed from the ventricles The free walls of the right and left ventricles were cut from the septum and divided into 3 layers (subendocardial middle, and subepicardial regions) of about equal thickness The ventricular septum was divided into three layers right middle and left The tissue from each region was placed in one or more vials weighed and counted in a well scintillation counter The radioactivity emitted from each nuclide was determined by the method of Rudolph and Heymann, modified by using the reference sample technique to calculate flows and by changing the constants used for differential spectrometry after recalibrating the counting equipment [7]

Regional myocardial flow was measured during control state (no left to right shunt) in each dog with 15 micron microspheres Pulmonary flow was then increased by 100 per cent 200 per cent, and 300 per cent (small moderate and large shunts) in random sequence In 5 dogs pulmonary flow was increased by 150 per cent and right ventricular hypertension (peak right ventricular pressure greater than 45 mm Hg) was produced by pulmonary arterial constriction With all shunts Ringer s lactate and/or fresh blood (125 to 275 ml) were infused to maintain left ventricular output and aortic pressure at control levels Changes in myocardial flow were determined with each dog serving as its own control

Total coronary vascular resistance was calculated from the equation resistance equals pressure difference/flow here the pressure difference was the coronary driving pressure, and flow was the myocardial flow (per 100 grams) as measured with radioactive microspheres This resistance calculation includes the effects of increased extravascular compression during systole as well as a coronary vasomotor tone The coronary driving pressure index (PI) of the right ventricle was calculated by planimetry of the area (per minute) between the aortic pressure tracing and the right ventricular pressure tracing Oxygen demand of the right ventricular myocardium was estimated from its tension time index (*TTI*)

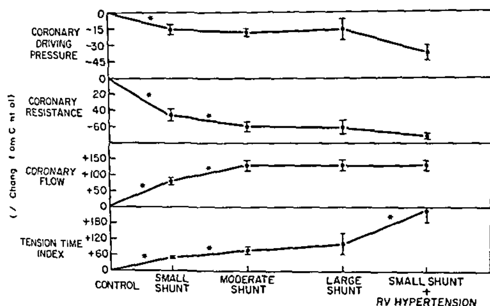


Fig 3 Per cent changes in right ventricular coronary hemodynamics in the four shunt groups Per cent changes are calculated from each dog s own control value Each point represent mean per cent change vertical brackets the standard error of the mean Asterisk indicates significant difference ($p < 0.05$) between adjacent points

124 per cent ± 13 This indicates that when right ventricular output and right ventricular pressure increased coronary vasomotor reserve was diminished

Changes in right ventricular coronary hemodynamics are shown in Fig 3 Coronary driving pressure progressively fell as right ventricular hypertension developed it averaged 4 37? ± 30 8 (S E) mm Hg per minute for the control group and 3 822 ± 366 mm Hg per minute 3 420 ± 276 mm Hg per min 3 360 ± 570 mm Hg per minute and 2 700 ± 440 mm Hg per minute in the 4 shunt groups respectively As coronary driving pressure fell coronary vasodilation occurred as reflected by the fall in coronary vascular resistance However coronary resistance did not fall significantly further in the groups with large or small shunts having right ventricular hypertension and this suggests that the coronary arteries were maximally vasodilated in these groups Right ventricular coronary flow increased as coronary resistance fell but in groups with right ventricular hypertension failed to increase further when coronary vascular resistance failed to change Right ventricular tension time index was increased by the elevation in right ventricular systolic pressure and the prolongation of systole with greater stroke volumes With shunts having only mild elevation in right ventricular pressure (small and moderate groups) coronary flow increased as the tension time index increased In shunts with right ventricular hypertension myocardial flow failed to increase further as the tension time index rose

To determine if we could predict from the pressure tracings when the right ventricular coronary arteries were no longer able to increase flow we related the right coronary driving pressure index (PI) to the right ventricular tension time index (TTI) that is estimated oxygen supply potential compared to estimated oxygen needs [2] This PI TTI ratio averaged 7 5 ± 0 72 (S E) in the control group and fell significantly ($p < 0.05$) with small left to right shunts but thereafter did not significantly change averaging 3 5 ± 0 60 3 7 ± 0 46 and 3 4 ± 0 86 respectively In the group with small shunts and right ventricular hypertension the PI TTI ratio fell to 1 7 ± 0 29 the difference from the other shunt groups being just above the conventional level of significance ($p < 0.10$)

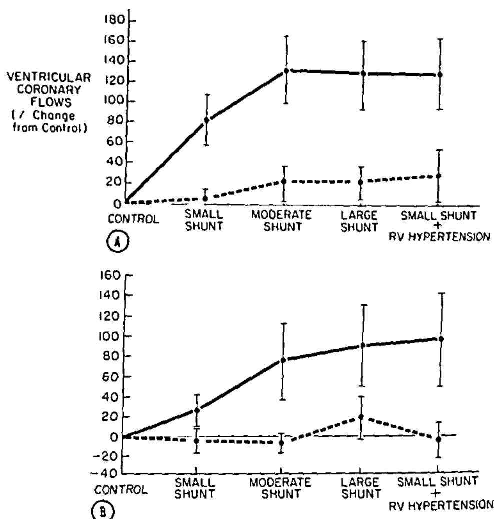


Fig 2 A and B Per cent changes in myocardial blood flow per gram to the free wall (A) and septal region (B) of the right (*solid line*) and left (*dashed line*) ventricles in the four shunt group Per cent change is calculated from each dog's own control value Small moderate and large shunts had pulmonary flow increased by 100 to 150 per cent 200 per cent and 300 per cent respectively RV hypertension is defined as right ventricular peak pressure above 45 mm Hg Each point represents mean per cent change vertical brackets the standard error of the mean

tricular peak pressure greater than 45 mm Hg) Coronary flow to the left ventricular free wall and the left side of the septum did not change significantly from control Changes in flow to the right and left portions of the ventricular septum resembled those to their respective free walls (Fig 2) The regional distribution of myocardial flow within the free walls of both ventricles as reflected by the ratio of subendocardial flow subepicardial flow (per 100 Gm) did not change significantly (Table II) The distribution of coronary flow between the ventricles did change for the control group myocardial flow (per 100 Gm) to the free wall of the right ventricle was 60 per cent of that in left ventricle In all of the shunt groups myocardial flow (per 100 Gm) to the free wall and septal regions of the right ventricle equalled or exceeded that to the left ventricle This change in coronary flow distribution was due to the increase in right ventricular coronary flow since left ventricular coronary flow remained unchanged

To estimate changes in coronary vasomotor reserve we measured the reactive hyperemic response of the right coronary artery at different right ventricular outputs In controls the occlusive coronary flow debt was repaid by 150 per cent ± 9 7 (S E) whereas with progressively larger shunts it averaged 121 per cent ± 10 110 per cent ± 12 127 per cent ± 14 and with small shunts and right ventricular hypertension

Coronary flow to the septal portion of the right ventricle increased significantly with greater right ventricular volume loads With effective autoregulation this indicates that septal myocardial oxygen consumption increased and suggests that septal contraction plays an important role in maintaining right heart output Other studies have suggested that the ventricular septum is responsible for maintenance of right ventricular performance following functional removal of the right ventricular free wall[14,15] Most recently Brooks and co workers[15] reported that complete occlusion of the right coronary artery in dogs caused no change in cardiac output or right ventricular pressure but that with the added stress of elevated right ventricular pressure right heart failure occurred In the present study once right ventricular pressure became elevated septal coronary flow failed to increase further This suggests that right ventricular hypertension may cause myocardial compression of coronary vessels within the ventricular septum thereby impeding coronary flow to this region

One purpose of this study was to determine if acute right ventricular volume loads exhaust right ventricular coronary reserve With small left to right shunts a slight increase in right ventricular pressure reduced coronary driving pressure however coronary flow was increased by vasodilatation as indicated by the fall in coronary vascular resistance (Fig 3) In fact the maximal increase in right ventricular myocardial flow occurred after right ventricular output was increased by 200 per cent (Fig 2) With larger left to right shunts or when right ventricular systolic hypertension developed myocardial flow failed to increase further Under these circumstances coronary vascular resistance failed to fall further suggesting that the coronary vessels were fully dilated and that this compensatory mechanism could no longer increase coronary flow The decreased reactive hyperemic responses of the right coronary artery also indicated that coronary vasomotor reserve was reduced In previous studies of acute right ventricular hypertension alone we found that myocardial flow initially increased with relatively mild hypertension but failed to increase further with moderate hypertension[2] Aukland and co workers[3] also reported that right ventricular hypertension alone increased right ventricular myocardial flow but usually less 200 per cent of control This may be explained on the basis that right ventricular hypertension decreases coronary driving pressure and limits coronary flow We found that acute cardiovascular collapse characterized by precipitous fall in blood pressure and systemic flow frequently occurred at those levels of right ventricular hypertension at which myocardial flow failed to increase Under such conditions the greater myocardial oxygen needs were not met by increased oxygen supply and resulted in relative coronary insufficiency In the present study myocardial flow failed to increase further with greater pressure and volume loads suggesting that an acute left to right shunt with right ventricular hypertension may also result in relative coronary insufficiency

It would be most helpful if acute cardiovascular collapse secondary to right ventricular hypertension could be predicted from hemodynamic data In our study of acute right ventricular hypertension alone we found the relationship between the right coronary artery driving pressure index and its tension time index was useful in predicting when right coronary vessels were unable to increase flow[2] This PI TTI ratio compared the pressure aspect of myocardial oxygen supply to the pressure aspect of myocardial oxygen need The relationship between the tension time index and myocardial oxygen uptake however is affected by changes in inotropic state heart rate and ventricular geometry and volume In the present study right ventricular diastolic pressure increased significantly with the acute changes in right ventricular output and indicated that right ventricular volumes probably increased Under such circumstances the tension time index may not reflect the effect of larger right ventricular volume on true wall tension and hence probably underestimates changes in myocardial oxygen need In the acute right ventricular hypertension study right ventricular myocardial flow failed to increase when the PI TTI ratio averaged 2 4 ± 0 27

Discussion

To our knowledge this is the first report describing the effects of acute right ventricular volume and pressure overloading on regional coronary flow. The present study provides evidence that coronary flow to the right ventricle is predominantly influenced by factors which alter pressure work rather than flow work and suggests that wall tension, as in the left ventricle, is probably one of the main determinants of oxygen need and thus regional coronary flow. It is important to consider how tension in the right ventricular wall changes with different pressure and volume loads.

Theoretically, according to the Laplace equation, wall tension is directly proportional to both cavity pressure and radius of curvature. Assuming that the right ventricular free wall is nearly hemispherical, then if peak pressure is doubled at constant radius, wall tension doubles. On the other hand, if stroke volume is doubled at constant peak pressure, only a small increase occurs in the radius of curvature and therefore there should be only a small increase in wall tension. This is what was found in the left ventricle by Braunwald and associates[10]; changes in left ventricular peak pressure resulted in greater alterations of myocardial oxygen consumption than did changes in cardiac output. When cardiac output was increased by 100 per cent and 200 per cent at constant peak left ventricular systolic pressure and heart rate, coronary flow increased approximately 10 per cent and 20 per cent, respectively (calculated from their Fig. 5). This is consistent with the study of Taylor and colleagues[11] who found that when left ventricular stroke volume doubled at constant peak pressure, peak wall tension increased by only 18 per cent.

In the present study when right ventricular output was increased by 100 per cent and 200 per cent, myocardial flow increased by 81 per cent and 134 per cent (Fig. 2). Right ventricular systolic pressure concurrently increased from 27 mm. Hg to 38 mm. Hg, indicating that right ventricular myocardial flow might have increased from the effects of greater pressure as well as from the effects of the larger ventricular output. Unfortunately, in the present study we could not determine the extent to which right ventricular volume overload alone increased right ventricular myocardial flow. However, in recent studies of acute right ventricular hypertension we found that when right ventricular systolic pressure increased in a similar fashion to the present study (from 26 mm. Hg to 37 mm. Hg), right ventricular myocardial flow (per 100 grams) increased from 65.7 ± 6.2 to 79 ± 7.2 ml. per minute (mean and standard error).[2] The latter flow value is not significantly different from the average right ventricular myocardial flow values obtained in groups with small and moderate shunts (78.8 and 65.4 ml./min./100 Gm.). These data suggest that, like the left ventricle, the increase in ventricular pressure was principally responsible for the increase in right ventricular coronary blood flow.

This study demonstrates that an increased volume load to the right ventricle resulted in an increase in right ventricular myocardial flow while left ventricular myocardial flow remained unchanged (Fig. 2). Earlier studies have shown that coronary flow to the right and left ventricles may vary independently, each being determined mainly by the pressure load of the respective ventricle.[2,3] Changes in the interventricular distribution of coronary blood flow therefore seem to reflect the work loads of the respective ventricles rather than the anatomical distribution of the coronary arteries. In dogs the left coronary artery supplies approximately one third of the right ventricular free wall.[12] As the pressure and volume load of the right ventricle increased, a greater proportion of total coronary flow went to the right ventricle presumably through both the right and left coronary arteries. If the changes in regional coronary flow resulted from altered sympathetic tone, then an increase in left coronary flow might be expected to increase myocardial flow in both the left and right ventricles. However, left ventricular myocardial flow did not change significantly, indicating that coronary vascular resistance maintained left ventricular flow in accordance with its metabolic requirements. This suggests that autoregulation of coronary flow is regional, being determined by regional metabolic factors

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(S E) whereas in the present study myocardial flow failed to increase further when this ratio averaged 3 7 ± 0 65 (moderate shunt group) Since the denominator of this ratio underestimates myocardial oxygen needs in this acute shunt study it seems reasonable to expect the ratio to be higher at the point where coronary flow is limited Although less sensitive in the case of acute ventricular volume changes the ratio of PI TTI may provide a means for indirectly assessing right ventricular coronary reserve in the presence of acute left to right shunts

Our results obtained with acute right ventricular volume overload in open chest anesthetized dogs cannot be applied directly to patients with chronic right ventricular overload and ventricular hypertrophy Not only will there be differences in autonomic and humoral influences but in the hypertrophied ventricle the thicker wall reduces wall tension for any ventricular pressure and radius[16] Furthermore in congenital lesions there could be more myocardial vascularity and thus differences in pressure flow relations in the regional coronary bed The importance of these differences between acute and chronic right ventricular volume overloads has not been evaluated but in one study of patients with left ventricular volume overloads Frank and colleagues[17] reported that an increase in myocardial oxygen consumption occurred only in association with increases in the left ventricular tension time index They suggested that in shunt lesions the stimulus which results in an increased metabolic demand of the myocardium is best described as a pressure overload If this is true also of right ventricular volume overloads, then the principles found in the present study even if not the numerical results, may well apply in human disease

Summary

In this study of acute right ventricular volume overloading in anesthetized dogs right ventricular coronary blood flow increased probably in response to the effect of increased right ventricular pressure on myocardial oxygen needs Left to right shunts with small elevations in right ventricular pressure had compensatory coronary vasodilatation which increased coronary flow However shunts with right ventricular hypertension had no further fall in coronary resistance and failed to have an additional increase in coronary flow This suggests that with acute right ventricular volume overloading the presence of right ventricular hypertension increases myocardial oxygen needs but limits the ability of the coronary vessels to increase flow Should myocardial oxygen needs increase and the coronary vessels be unable to increase myocardial perfusion relative coronary insufficiency may occur

We gratefully acknowledge the technical assistance of Elizabeth Shapkin and Kip Saunder

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Experimental myocardial infarction in the closed-chest dog Controlled production of large or small areas of necrosis

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Because it has been impractical to study many aspects of coronary artery disease in man investigators have used animal models particularly the dog Open chest methods of obstructing coronary arteries have been employed most frequently Early attempts involved simple ligation of coronary arteries[1] or injection of a starch suspension into the aortic root Because of the high mortality rate attendant upon sudden occlusion of coronary arteries methods of gradual yet progressive, obstruction of vessels were developed Ameroid constrictors[3,4] inflatable balloons[5] adjustable hydraulic occlusive devices[6] microspheres injected via an indwelling catheter in the left coronary artery[7] sutures and snares around the coronary vessels[8-11] and thrombogenic wires introduced through the wall of the coronary artery[12] have been employed to this end The need for thoracotomy is a major drawback of these techniques and prompted the development of several closed chest methods

The availability of selective angiographic methods has greatly simplified the introduction of catheters into the coronary arteries Selective embolization of the coronary artery with wire coils[13] or steel cylinders[14,15] steel balls,[16] lead foil[17] radiopaque spheres[18,19] microspheres[20-2] lycopodium spores[3] Kifa catheter tips[4] plastic cones[25] thrombus[15] or mercury[26-9] has been accomplished Furthermore ischemia has been induced by wedging catheters into distal coronary arteries[30-32] and inducing thrombus formation with current passing from an electrode introduced selectively into a coronary artery[33,3]

We have modified one of these methods—that of Hammer and Pisa[4]—to allow either immediate or delayed occlusion of a coronary artery to permit assessment of the effect on mortality rate and infarct size

Method

Adult mongrel dogs are anesthetized with sodium pentobarbital (30 mg per kilogram of body weight) After obtaining a control coronary angiogram with Reno

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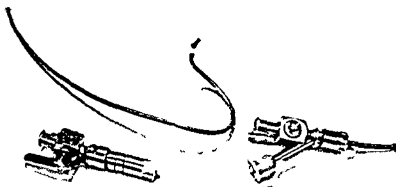


Fig 1 Coaxial catheter for embolization of coronary arteries with hollow plugs

grafin[R] 76 (Squibb) one of two catheter systems is introduced into the femoral artery

I Delayed occlusion To produce a delayed occlusion a hollow plug is selectively embolized into the coronary artery The coaxial catheter system consists of an outer preformed red Kifa* catheter (6 6 Fr) similar to that used for coronary angiography and an inner Teflon catheter† (outer diameter 0 039 inch) (Fig 1) The latter passes into the Kifa catheter through an adaptor with sidearm and extends enough beyond the tip of the Kifa catheter to carry a 3 to 5 mm length of tapered red Kifa tubing The assembled catheter system is then introduced into the femoral artery and maneuvered into either the left anterior descending (LAD) or left circumflex (LCf) coronary artery or first septal Localization is documented fluoroscopically with contrast medium injected through the Teflon catheter Just prior to the release of the plug an infusion of intravenous lidocaine is started which delivers approximately one mg per minute While holding the outer Kifa catheter firmly and preventing it from moving the inner Teflon catheter is gradually withdrawn into the outer catheter and the plug is thus released into the coronary artery After embolization the animal s rhythm is monitored for approximately 30 minutes Ventricular ectopic beats have rarely been observed but when present have been treated with successive 25 mg intravenous lidocaine boluses After 30 minutes the lidocaine drip is discontinued and the animal is treated prophylactically with lidocaine 100 mg subcutaneously propranolol 3 to 4 mg intramuscularly and ampicillin 0 5 Gm intramuscularly

II Immediate occlusion In this catheter system an 0 021 inch guide wire replaces the Teflon catheter inside the outer preformed Kifa catheter (Fig 2) The plug is heat sealed at one end and is impaled on the tip of the wire The catheter system is maneuvered into the appropriate coronary artery and position is verified by dye injection through the Kifa catheter and around the wire Prior to release of the plug a 50 mg bolus of lidocaine is administered intravenously and the *lidocaine infusion* is begun at the rate of 1 mg per minute The wire is then withdrawn into the outer Kifa catheter and the plug is released into the vessel The animal s rhythm is carefully monitored for 30 minutes Salvos of ventricular ectopic beats are quite common in the initial 30 minutes and 50 mg boluses of lidocaine are injected intravenously as soon as ectopic activity is observed and periodically until it subsides It is uncommon for the ectopic beats to persist for longer than 30 minutes After this period the intravenous infusion is stopped and the animal is treated prophylactically as above After the procedure all catheters are removed the femoral artery is ligated and the tissues are sutured

Two to four weeks after the occlusion all animals were restudied with coronary

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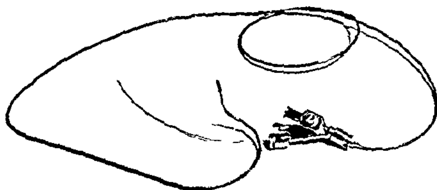


Fig 2 Coaxial catheter for embolization of coronary arteries with solid plugs A guide wire has replaced the inner Teflon catheter

Table I Survival related to type of plug

Plug	Vessel		
	LAD*	LCf	First septal
Hollow			
Survived	22	—	2
Died	3	—	—
Solid			
Survived	8	2	1
Died	2	—	—

*Abbreviations LAD = left anterior descending artery LCf = left circumflex artery

Table II Infarct size related to type of plug

Dog	Vessel	Plug	% infarct
242	LAD*	hollow	0
338	LAD	hollow	16
342	LAD	hollow	0
344	LAD	hollow	0
419	LAD	hollow	0
475	LAD	hollow	5
520	LAD	hollow	6
569	LAD	hollow	5
Average			4 ± 2
48	LAD	solid	14
162	LAD	solid	24
176	LAD	solid	28
184	LAD	solid	18
339	LCf	solid	17
748	LAD	solid	21
Average			20 ± 2

*Abbreviations LAD = left anterior descending artery LCf = left circumflex artery

angiography After acute interventions (to be reported elsewhere[16]) the animals were killed and the hearts were excised The ventricular cavities were filled with gauze sponges to prevent collapse of the ventricles and the hearts were frozen The hearts were sectioned every 4 to 5 mm from apex to base The slices were photographed and the areas of visible infarction and total left ventricular surface were measured from the photographs by planimetry It was quite simple to outline the necrotic areas which had a different texture and color compared to the surrounding myocardium The ratio of infarct size to total left ventricular area was calculated

Results

Hollow plugs were embolized into the coronary arteries of 27 dogs and solid plugs were used in 13 animals (Table I) There was an 11 per cent mortality rate associated with the hollow plugs two dogs succumbed within one hour and one died after 48 hours Two dogs with occlusive plugs died within one hour There were no late deaths All animals except one had well developed collateral vessels by the time of the repeat coronary angiogram (Fig 3) Twenty three of the surviving 24 dogs with hollow plug emboli had angiographic documentation of complete occlusion of the embolized vessel The remaining dog had a patent LAD after three weeks despite apparent normal clotting mechanisms A second hollow plug in the LAD resulted in complete occlusion

The hearts of 14 dogs were serially sectioned, eight with hollow and six with solid



Fig 3 A and B Selected films from coronary angiograms done before (*A*) and three weeks after embolization (*B*) of the left anterior descending (LAD) coronary artery with a hollow plug The LAD is totally occluded at the level of the plug and the distal LAD is filled retrogradely by left to-left collaterals from the left circumflex and diagonal branches

plugs (Table II) Seven of the eight animals with delayed coronary artery occlusion had either no or minimal visible areas of infarction (≤ 6 per cent) The eighth dog had 16 per cent of the left ventricle infarcted Of animals with solid plugs all had transmural damage and an area of infarct ranging from 14 to 28 per cent (average 20 ± 2 per cent) of the measured left ventricular cross sectional surface (Fig 4) The difference in infarct size in dogs embolized with hollow plugs compared to those embolized with solid plugs is highly significant ($p < 0.001$)

After embolization of a hollow plug in two dogs coronary angiography was performed every 15 to 30 minutes until the plug occluded Occlusion occurred between the fourth and fifth hours after embolization

Discussion

Although animal models of coronary artery disease are not ideal many investigators have occluded coronary arteries in animals in an attempt to simulate some of the sequelae of naturally occurring coronary artery obstruction Open-chest techniques require thoracotomy with its added mortality rate and inconvenience Adhesions between pericardium anterior chest wall and myocardium make subsequent reoperation for study of collaterals or myocardial function more difficult and occasionally impossible Furthermore the interruption of neural structures during coronary dissection may affect subsequent physiologic responses Most closed chest methods require equipment not readily available in most radiology and catheterization laboratories wire coils [13] steel cylinders [14,15] steel balls [16] lead foil [17] radiopaque spheres [18,19] or microspheres [20-22] The technique described above however uses only Kifa and Teflon catheters and guide wires which are readily available The technique is sufficiently versatile to allow for immediate or gradual occlusion with only minor alterations in approach No method previously described permits this choice

All described fluoroscopic methods save one[22] have used the carotid artery We have chosen the femoral approach Selective coronary catheterization is much easier using this route and our preformed cath



Fig 4 Serial cross sections of the left ventricle of a dog three weeks after embolization of the left anterior descending coronary artery with a solid plug. The macroscopic areas of necrosis are easily outlined. This dog had 24 per cent of its left ventricular cross sectional area affected by the abrupt deprivation of arterial blood

eters The femoral approach also allows the investigator to sacrifice both femoral arteries in the course of multiple angiographic, radioisotopic or other studies and use the carotid vessels in subsequent acute experiments However, if reflex control and neurologic function are to be undisturbed only one carotid artery can be sacrificed safely thus limiting the number of possible interval studies This is an important consideration in protocols employing multiple study points

There has been meager documentation of the extent of infarction by any of these methods Kordenat and associates[13] estimate 25 per cent infarction with wire coils lodged in the proximal LAD or LCf and 10 per cent infarction with coils in the distal vessels Dogs with an inflatable balloon encircling the LAD just past its origin had infarction of 22 to 49 per cent of the left ventricle[5] Schaper[37] has noted that immediate LAD occlusion produces infarcts ranging from 11 to 33 per cent of the left ventricular mass, depending on the measurement technique employed whereas approximately 50 per cent of dogs with gradual coronary occlusion from Ameroid constrictors have no infarcts Ninety per cent (7/8) of our dogs with hollow plugs had essentially no visible infarction of the left ventricle (average 2 per cent) Because of resorption of necrotic muscle these numbers likely underestimate the size of the infarcted area Four weeks after LAD occlusion the thickness of the left ventricular wall in the area of the infarct may be decreased by up to 50 per cent[37]

Serial coronary angiography suggests that the hollow plug is occluded by thrombus at approximately four hours The occlusion is unaccompanied by arrhythmias and often there is no characteristic change in the surface electrocardiogram This gradually progressive coronary artery stenosis creates an area of ischemic myocardium which apparently induces the enlargement of already existing collateral pathways[38,39] Although these existing collaterals are not sufficient to supply the total metabolic requirements of the involved area most probably they do serve a protective function and prevent significant areas of myocardium from becoming necrotic after complete occlusion of the embolized vessel This hypothesis is supported by the observation of Elliot and colleagues[39] who gradually narrowed the LCf of dogs over 3 to 4 day periods and observed progressive increases of collateral indices during the con

striction period and no or minimal evidence of infarction when the animals were killed Thus this preparation is ideal for the study of collateral vessels or viable potentially ischemic myocardium One surprising observation is the clear-cut protection afforded the dog by a relatively short period of gradually progressive stenosis before total coronary artery occlusion Further studies are required to define the minimal duration of stenosis necessary and the exact nature of this protection in biochemical and hemodynamic terms

The eighth animal with a hollow plug had 16 per cent of its left ventricular cross sectional surface area infarcted and it is postulated that the hollow plug thrombosed shortly after its embolization Those dogs with solid plugs in the LAD averaged 20 per cent infarction These animals were unable to profit from the enlargement of existing anatomic but non functional collateral pathways before the myocardium was irreversibly damaged [40,41]

This model is suitable for examining post infarction hemodynamics contractility therapeutic modalities etc It is reasonable to suppose that larger infarcts and even shock models might be created by more proximal coronary artery obstruction with wider Kifa catheter plugs or with multiple plugs

Summary

In order to embolize the coronary arteries a closed-chest technique was employed using fluoroscopically positioned catheters introduced selectively into the coronary arteries Plugs made of catheter material were extruded directly into the coronary lumen Small alterations in the coaxial catheter system permitted the use of either hollow or solid plugs with production of delayed or immediate coronary artery occlusions respectively With hollow plugs the mortality rate was 11 per cent An average of 4 ± 2 per cent of the left ventricular cross sectional area was infarcted Solid plugs were associated with a mortality rate of 15 per cent and infarction of 20 ± 2 per cent of the left ventricle Using this method it is therefore possible to create reproducible controlled infarct sizes in dogs enabling a careful study of collaterals ischemic myocardium and therapeutic interventions

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Protection against epinephrine induced myocardial necrosis with clofibrate

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Recent clinical trials have suggested that clofibrate exerts a protective effect against myocardial infarction and death among middle aged men an effect that may be independent of the lowering of serum lipid levels by the drug [1-3] Clofibrate has been demonstrated to decrease platelet adhesiveness among men with nonacute ischemic heart disease [4-8] It is possible that the precipitating event in acute myocardial infarction may be the sudden occlusion of a narrowed coronary artery by an intra vascular platelet aggregate [9] and it is possi ble that clofibrate may exert its protective effect by inhibiting such intravascular platelet aggregation

Sympathetic catecholamines will cause platelet aggregation *in vitro*[10-12] and infusion of norepinephrine will cause intravascular aggregation of platelets in the small ves sels of the heart [13] Rats subjected to stress will develop intravascular platelet aggre gates in myocardial vessels [14] Pretreatment of dogs with the antiplatelet aggregating drugs aspirin and dipyridamole will prevent the occurrence of the widespread myocar dial necrosis usually seen after epinephrine infusion [15] To determine if clofibrate will exert a similar protective effect against epinephrine induced cardiac necrosis sug gesting that clofibrate might interfere with epinephrine induced platelet aggregation the following studies were performed

Material and methods

Twenty two mongrel dogs weighing 15 to 20 kilograms were studied Twelve dogs were pretreated for 5 days with clofibrate (Atromid S) 500 mg orally twice daily Ten control dogs were not pretreated Aortic pressure and the peripheral electro cardiogram were monitored as previously described [15]

Epinephrine was infused intravenously at a rate of 4 μg per kilogram of body weight per minute for 4 hours The dogs were killed 1 week after infusion the hearts were removed and fixed in formalin and histo logic sections of the left ventricle were stained with hematoxylin and eosin and examined for presence or absence of necro sis The degree of myocardial damage was graded on a scale of 0 to 3+ as previously described[15] 3+ if extensive areas of con

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In another study from this laboratory it was shown that epinephrine induced myocardial necrosis can be prevented by pretreatment with drugs known to inhibit platelet aggregation[15] In the present study we have demonstrated that epinephrine induced myocardial necrosis can be prevented similarly by pretreating with oral clofibrate a drug which has been described as possibly being effective in the long term treatment of ischemic heart disease in man It is possible that clofibrate exerts its protective effects by an alteration of platelet function or of the response of platelets to exposure to sympathetic catecholamines

Over the past decade a number of investigators have demonstrated effects of oral clofibrate on platelet function in patients with ischemic vascular disease Platelet adhesiveness and platelet factor–3 activity are abnormally increased in patients with nonacute ischemic heart disease[26,27] The cause of these thrombogenic changes in platelet function is unknown A number of investigators have indicated that these platelet function abnormalities are at least partially corrected by administration of clofibrate Oral clofibrate administration has been found to significantly reduce both platelet adhesiveness and platelet aggregation in patients with nonacute atherosclerotic disease both when administered alone and when administered as Atromid a combination of clofibrate with androsterone[4,8,28,29] The androsterone may or may not enhance this effect[5,7] Some investigators have observed that this effect of clofibrate on platelet adhesiveness and aggregation appears to be independent of changes in serum lipid levels[4,6,8] Human platelet factor–3 activity and availability may also be reduced by treatment with oral clofibrate[30]

Although most reports indicate that oral clofibrate interferes with platelet aggregation in man this observation is not unanimous One study of platelet adhesiveness was unable to confirm the reported effects of oral clofibrate[31] and another study found that the reduction of platelet adhesiveness was gradually lost after two months treatment[32] Nevertheless the antiplatelet aggregating action of clofibrate indicated by most human studies and the similarity of the results of the present dog study with those of the previous study which used known antiplatelet aggregators suggest that the present results can be explained by clofibrate s interference with platelet aggregation

It is also possible that the protective action of clofibrate observed in dogs is due to interference with vascular effects of epinephrine (other than vasoconstriction) that may result secondarily in the formation of platelet aggregates Shimamoto and colleagues[33,34] have demonstrated that epinephrine will cause endothelial edema and release of a thromboplastic and platelet attracting substance in rabbit aortas Thus it is possible that catecholamine induced platelet aggregation is mediated by endothelial damage and/or vascular release of a humoral platelet aggregator Numerous studies have demonstrated the platelet aggregating tendency induced by other types of endothelial damage[35,37] Rowsell and associates[38] however have shown that the presence of a subjacent endothelium or vessel wall is not essential for the thrombogenic effect of epinephrine *in vivo* Shimamoto s group[34,39] has demonstrated that the platelet consuming effect of intravenous epinephrine can be blocked in man and in animals by pretreatment with a variety of unrelated compounds It is possible that the protective effect of clofibrate observed in the present study might be due to a similar block of the vascular effects of epinephrine

In addition to its effects on serum triglycerides and cholesterol oral clofibrate also tends to reduce serum phospholipid levels[40] Mustard and associates[41] have reported that alterations in the concentrations of various specific serum phospholipids can have varying effects on the tendency of platelets to aggregate Thus it is conceivable that the protective effect of clofibrate observed in this study was mediated by alterations in the plasma lipid constituents

The protection against epinephrine induced necrosis by pretreatment with clofibrate demonstrated in this study implies that the drug exerts a direct or indirect inhibiting effect on epinephrine induced intravascular platelet aggregation in dog hearts Such an effect may have applica

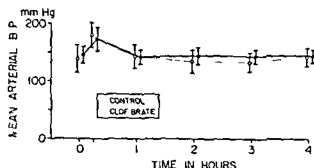


Fig 1 The effect of epinephrine infusion on the mean arterial blood pressure of control dogs and those pretreated with clofibrate

fluent necrosis (destruction of myocardial cells presence of round cell infiltration and early fibrosis) were present, 2+ if extensive areas of necrosis without confluence were found, 1+ if small areas of necrosis more than 3 per slide were present on 6 slides and 0 if no areas of necrosis were found on any of the slides Pretreated and control dogs were studied in random order, the grading pathologist (R O) did not know which or how many animals had been pretreated

Results

The blood pressure responses to the epinephrine infusions were similar to those previously described by Moss and colleagues[16] After an early rise the pressure usually fell to near the control level at 1 hour and remained there for the duration of the infusion (Fig 1) Systolic diastolic and mean pressures of the clofibrate group were not significantly different from those of the control group at comparable times during the infusions (Student t test)

On histologic study 1 week after infusion (Table I), all dogs in the control group had evidence of cardiac necrosis 6 dogs with 3+, 2 dogs with 2+, and 2 dogs with 1+ necrosis Among the 12 dogs pretreated with clofibrate 3 dogs had 2+ necrosis and 2 dogs had 1+ necrosis Seven dogs had no evidence of necrosis Comparison between the pretreated group and the control group with respect to the presence or absence of histologic evidence of necrosis showed that the findings were statistically significant ($p < 0.01$ by chi square analysis)

By the end of the infusion, few dogs had significant electrocardiographic changes

Table I Histologic cardiac findings 1 week after infusion

	Extent of necrosis*			
	3+	2+	1+	0+
Control group (10 dogs)	6	2	2	—
Clofibrate group (12 dogs)	—	3	2	7

*Necrosis is graded 1+ to 3+ Grade 0 indicates no evidence of necrosis. The difference between the 2 groups is statistically significant (see text)

One dog in the control group had an acute inferior wall myocardial infarction and 2 others had left axis shifts These 3 dogs all had 3+ necrosis on histologic examination One pretreated dog with 1+ necrosis had a right axis shift All other dogs had either no electrocardiographic changes or only non specific T wave changes

Discussion

Production of diffuse patchy myocardial necrosis by catecholamine administration has been known since 1907[17] Since then this effect has been described following infusions of epinephrine norepinephrine or isoproterenol in a variety of animals and in man[18-23] Similar myocardial changes have been demonstrated in the majority of patients who die with pheochromocytoma[24] In a study previously reported from this laboratory it was demonstrated that norepinephrine infusions in doses known to cause such myocardial necrosis will result in intravascular platelet aggregation in the dog heart Intravascular platelet aggregates were associated with changes of early myocardial necrosis before there was electron microscopic evidence of fibrinous thrombus formation[13] In 1967 Jorgensen and colleagues[5] demonstrated that intravascular platelet aggregates in the pig heart induced by intracoronary infusion of adenosine diphosphate will cause transient obstruction of the microcirculation leading to diffuse myocardial necrosis[25] Thus, it appears that myocardial necrosis can be induced directly by intravascular aggregation of platelets

clofibrate and 10 dogs not pretreated were infused with epinephrine 4 μg per kilogram of body weight per minute After killing the dogs 1 week later the degree of myocardial damage was assessed histologically All control dogs had myocardial necrosis 6 with 3+ 2 with 2+ and 2 with 1+ necrosis Seven of the 12 pretreated dogs had no necrosis 2 had 1+ and 3 had 2+ necrosis These differences are statistically significant ($p < 0.01$) Previous studies have shown that norepinephrine infusions will induce intravascular platelet aggregation in the dog heart and pretreatment with antiplatelet aggregating agents will prevent epinephrine induced myocardial necrosis The demonstration of oral clofibrate s protection against epinephrine induced myocardial necrosis suggests that clofibrate may exert a similar antiplatelet aggregating effect It is possible that oral clofibrate exerts a beneficial effect in human coronary artery disease via a similar mechanism

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tions to human disease. Acute myocardial infarction has been described to occur commonly following prolonged emotional stress.[42,43] During stress the endogenous secretion of sympathetic catecholamines is increased in man.[44] This laboratory has recently reported the occurrence of extensive intravascular platelet aggregation in the hearts of rats sacrificed following a period of prolonged physical and emotional stress.[14] It is possible that the higher levels of circulating catecholamines associated with human emotional stress in combination with pre-existing atheromatosis may lead to an enhanced tendency to form intravascular platelet aggregates and platelet thrombi. If one of these thrombi forms at or embolizes to an area of a coronary artery already narrowed by an atherosclerotic plaque, occlusion of the lumen and ischemia or infarction may ensue. Platelet thrombi are fragile and hence, typically, such infarction would not necessarily be associated with identifiable thrombosis on postmortem examination[9] and thus would be consistent with the low pathological incidence of coronary thrombosis reported in acute fatal myocardial infarction.[45] Therefore one might anticipate that pharmacologic agents which inhibit catecholamine induced platelet aggregation would be effective in reducing the incidence of ischemic episodes in patients with coronary artery disease subject to emotional stress.

In this regard it is noteworthy that three different long-term studies recently have reported that oral clofibrate reduces the incidence of myocardial infarction in patients with and without coronary artery disease. It is claimed that clofibrate's protective action in these patients bears little relation to its lipid lowering effect. Krasno and Kidera[3] reported 518 men treated with 500 mg. of clofibrate 4 times daily for 39 months and compared them to 550 male controls pair-matched for risk factors of coronary artery disease. Ninety-eight per cent of their patients were free of signs or symptoms of coronary artery disease at the start of observation. The incidence of episodes of angina pectoris and myocardial infarction were monitored in both groups and were found to be significantly higher in the control group than in the treated group. These differences were significant to the 0.1 per cent level ($p < .001$). Those hyperlipidemic men treated with clofibrate who failed to sustain a reduction of their serum lipid levels nevertheless demonstrated no clinical or electrocardiographic evidence of myocardial infarction in contrast to a 58 per cent incidence of infarction among the hyperlipidemic controls. In the United Kingdom, physicians of the Newcastle upon Tyne region[1] reported a 5 year double-blind study of 244 patients with ischemic heart disease treated with clofibrate 1.5 to 2.0 Gm. daily and compared them with 253 patients treated with placebo. The incidence of cardiac deaths was significantly lower in the treated group ($p = 0.02$) as was the incidence of first nonfatal myocardial infarction ($p < 0.05$). Those male patients who sustained cardiac death or infarction had had at least as adequate a reduction of serum lipid levels in response to treatment as those who had no such incidents. The Scottish Society of Physicians[2] also reported a 6 year study of patients with pre-existing coronary artery disease. Three hundred and fifty patients were treated with clofibrate 1.6 to 2.0 Gm. daily and were compared with 367 similar patients treated with placebo. Clofibrate significantly reduced the incidence of cardiac death in patients entering the study with a history of angina pectoris ($p < 0.01$) and the incidence of myocardial infarction in patients entering with a history of both angina and previous infarction ($p < 0.05$). There was no significant relationship between the response of serum cholesterol to clofibrate and the incidence of events either in patients with angina or in those with infarction.

It is quite possible that the beneficial effects of oral clofibrate noted in all these three studies are related to an inhibitory effect upon intravascular platelet aggregation. It is hoped that further clinical trials using known inhibitors of platelet aggregation will be forthcoming.

Summary

To investigate the possibility that oral clofibrate interferes with catecholamine induced platelet aggregation and myocardial necrosis, 12 dogs pretreated with oral

Case reports

Congenital absence of the circumflex coronary artery

Clinical and cinearteriographic observations

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The current emphasis on the surgical management of occlusive coronary artery disease has necessitated a deeper understanding of the anatomy of the coronary vessels. Precise knowledge of this anatomy becomes critical in the preoperative interpretation of coronary arteriograms. Congenital coronary anomalies per se have received modest attention in the clinical literature, with the exception of coronary vessels arising from the pulmonary artery.

The variations in normal coronary anatomy and the specific congenital anomalies have been catalogued by a number of authors.[1,2,5,7,11] Blake and colleagues[2] have grouped all anomalies into three categories which are based on the degree of impaired function encountered and the extent of the technical impediment for the cardiovascular surgeon.

The most commonly described variation of the left circumflex artery occurs in 1 to 2 per cent of cases in which it originates from the proximal portion of the right coronary artery or from the right coronary cusp.[2,3,5,8,11] No reference is made to complete absence of the left circumflex artery.

This report presents two cases which we believe represent congenital absence of the left circumflex artery with all other vessels being normal.

Case reports

Case 1. Mr. M. M. is a 33-year-old Caucasian man, machinist, who was referred to Rush Presbyterian-St. Luke's Medical Center for evaluation of coronary artery disease. He was in apparent good health until March 1972, at which time he developed substernal, non-radiating, dull chest pain while sitting at home. The pain lasted for approximately five minutes and was associated with no other symptoms. The following day the pain recurred and was associated with some shortness of breath. No specific measures were taken and he recovered. However, in April 1972 the substernal discomfort recurred and was sufficiently severe that he was admitted to a local hospital where an electrocardiogram was read as showing an anteroseptal myocardial infarction. Pain recurred in May and September 1972 and the patient was hospitalized on each occasion. The elec

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Fig 2 Lateral view of the right coronary artery which is entirely normal and supplies long branches to the posterior wall



Fig 3 Lateral project on howing a double platinum pacing catheter in the right ventricular chamber The main left coronary artery is visualized The ost um of the vessel is po ter orly located The vessel i cont nuou with the left anterior descending artery which appear to be ent ely normal A true main circumflex artery is not vi ualized



Fig *4A* Anteroposterior projection of the main left coronary artery injection The first branch of the left coronary artery is seen This small vessel courses laterally in the usual area of distribution of the left anterior descending

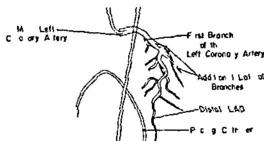


Fig *4B* Detailed llu tration outlining the various branches of the left coronary artery as shown in Fig *4A*

35 mm film wa exposed at 60 frames per second w th kilo oltage and m lliamperage automatically regulated The film was proce sed in a Kodak Versa mat film processor

The right coronary artery was ent rely free of occlu ive a d mural d sease and was shown to upply a large port on of the posterior surface of the heart (Fig 2) The main left coronary artery demonstrated a more posterior or gin and cont nued as the anterior descend g artery which was normal No charac teri tic circumflex branch could be identif ed (Fig 3) Mult ple selective cu p injections were performed and no accessory ostia were vi ualized The earliest branches of the left anterior descending artery did not follow the typical course of the main circumflex artery when seen in the posteroanterior projection (Fig 4*A* and *B*)

Case 2 Mr D M is a 50-year old Cauca ian man production engineer with a five year history of crampy precordial pain radiating to the left arm In 1968 he was hosp talized for 21 days for su pected myocard al infarction with no concrete evidence to upport that diagnos s Beginning in March 1972 he began to notice more frequent episodes of che t pain as often as two to three times daily These ep sodes were occa onally associated with nausea diaphoresis and dizzine however there was equivocal re sponse to nitroglycerine i osorbide d nitrate He had a history of mild hypertension for approximately five years and greater than 30-pack years of cigarette

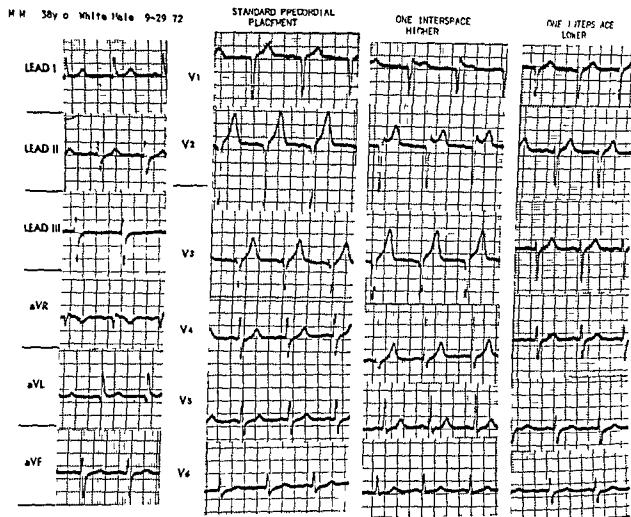


Fig *1* A 12 lead electrocardiogram and six precordial leads taken at three different intercostal levels (Case *1*) A normal progression of the R wave can be seen when the electrodes are placed one interspace below a standard location

trocardiograms were again interpreted as showing an anteroseptal myocardial infarction During these hospitalizations there were no enzyme changes and the patient had an inconsistent response to the administration of sublingual nitroglycerine Complete upper gastrointestinal and gall bladder radiologic survey were normal The physical examination was consistently within normal limits

The patient s father had maturity onset diabetes adequately controlled with diet There are no other significant features in the patient s family history The only other pertinent risk factor for coronary disease in this patient was a history of 40 pack years of cigarette smoking

On admission to the Rush Presbyterian-St Luke s Medical Center the physical examination was entirely normal Hemoglobin was 14 2 Gm per cent and complete blood count was normal The two-hour postprandial blood sugar was 100 mg per cent Uric acid serum cholesterol and triglyceride levels were normal The posteroanterior and left lateral chest x ray were also normal A 12 lead electrocardiogram at rest was within normal limits Precordial leads were taken at the standard level at one interspace higher and at one interspace lower (Fig 1) The high precordial sequence revealed a QS configuration in V_1 through V_3 with upward scooping of the ST segment in V_2 which had been interpreted earlier as consistent with anteroseptal myocardial infarction However the precordial sequence at the standard level showed an entirely normal progression of the R wave with concordant T waves The QR ST angle in the frontal plane was normal with a mean frontal QRS axis of −30 degrees The patient underwent a 44 step double Master s exercise test which revealed no changes A vectorcardiogram performed on a Hewlett Packard (Model 1507A) vector programmer using the Frank lead system was interpreted as within normal limits

Selective coronary arteriography and left ventriculography were performed by the Seldinger method using Judkins Cordis catheters * Simultaneous biplane cinearteriography was performed employing Siemens† cine pulsed equipment with high resolution cesium iodide phosphor Kodak‡

*Cordis Corporation Miami Fla.

†Siemens Corporation biplane X ray units 35 mm variable speed Model BS100 Erlangen Germany

‡Kodak Linagraph Shelburst Estar AH Base Type 2476 Oakbrook, Ill



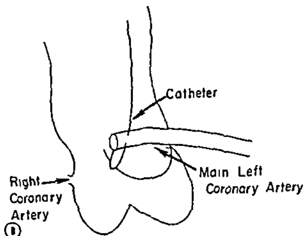


Fig 8A and B A Aortic root opacification showing a normal aortic valve and no accessory coronary ostia Again the main left artery gives off no circumflex branch and is continuous with a normal left anterior descending artery B Detailed illustration outlining the anatomy of the aortic cusp and its relationship to a single ostium of the left coronary artery

cardiogram were normal Treadmill exercise was attempted using a standard protocol After 1 minute at 0 per cent incline and 3 m p h the patient began to experience arm pain and the exercise was interrupted The heart rate at rest was 50 beats per minute and was increased to 68 with no evidence of myocardial ischemia at this point A vectorcardiogram was also performed which was normal (Fig 5)

Coronary arteriography was performed The main left coronary artery originated more posteriorly than usual and continued as the left anterior descending which was entirely normal No circumflex artery was identified (Fig 6) Selective left cusp injections (Fig 7) and an aortic root angiogram (Fig 8A and B) demonstrated the unusual origin of the proximal vessel and the lack of accessory ostia The right coronary artery injection revealed a normal vessel with prominent posterior distribution (Fig 9)



Fig 9 Lateral view of the right coronary artery showing a markedly dominant distribution Reflux of dye into the cusp suggests no accessory ostia The vessel is entirely normal

Discussion

The incidence of anomalous branches of the left coronary artery is relatively rare In his compendium James[5] indicates that the only consistently occurring anomaly of the left circumflex is that in which the vessel originates from the main right coronary artery or from an accessory ostium in the right coronary cusp the former being more frequent In this setting the vessel travels posteriorly around the aorta to enter the atrioventricular groove[2 3 7 10] The defect is particularly frequent in patients with transposition of the great vessels[7] Our angiograms clearly exclude this possibility

Wenger and Peace[12] and Grossman and Adams[4] have reported cases of the diminutive left coronary syndrome. In these patients the circumflex artery is absent or is an insignificant vessel but the left anterior descending artery is also abnormal Again our angiograms exclude this possibility

The selective cusp injections in Case 1 and the aortic root injection in Case 2 effectively exclude the possibility of accessory origin of the left circumflex from the left coronary cusp which is seen in 1 per cent of cases[11]

In Case 2 total occlusion of the circumflex artery at the ostium seems unlikely in







Fig 5 Display of a normal vectorcardiogram obtained in Case 2



Fig 6 Lateral projection showing a bipolar pacing wire in the right ventricular chamber The main left coronary artery originates from an unusual posterior location in the left coronary cusp and is continuous with an entirely normal left anterior descending There is no identifiable main circumflex artery or ramus intermedius The posterior wall of the aorta and the coronary cusp is opacified by refluxed dye and no accessory ostia are visualized

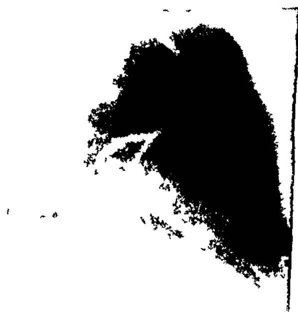


Fig 7 Lateral projection of a selective left coronary cusp injection showing no circumflex branch of the left coronary artery The main left coronary has an unusual posterior origin in the left coronary cusp

smoking There was no evidence of diabetes mellitus or gout but the family history was impressive The patient s father suffered three cerebrovascular accidents and his mother died at the age of 42 from cerebrovascular disease Two sisters and one brother have all had documented myocardial infarctions

The patient was admitted to the Rush Presbyterian-St Luke s Medical Center for further evaluation of his chest pain On admission the physical examination was completely normal Hemoglobin complete blood count serum electrolytes and enzyme levels were all normal Liver function studies serum cholesterol and serum triglycerides were also normal The upper gastrointestinal evaluation was normal Routine chest x ray and 12 lead electro-

Traumatic coronary arterial fistula

A case report and review of the literature

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Traumatic coronary artery fistulas are rare Ten cases have been reported previously[1-14] (See Table I) These cases elucidate the spectrum of problems in volved in managing this entity The present report discusses an additional case sum marizes the accumulated experience from the literature and emphasizes some of the more difficult management problems asso ciated with traumatic coronary arterial fi tula

Case report

E W a 24 year old man hero n addict was shot at close range with a 22-caliber bullet on July 18 1972 He was taken to a suburban hospital where hi vital signs were stable and chest x ray essentially normal except for the bullet which was shown to l e outside the chest wall beneath the right pectoralis muscles No heart murmur was initially heard An entrance and exit wound of the left biceps and an entrance wound in the left chest were observed On the thi d day he became febrile accumulated a marked r ght and left hemothorax and was noted for the first time to have a loud precordial murmur The pat ent was transferred to the Massachusetts General Hospital on July 21 1972 where he pre sented with a blood pressure of 120/70 mm Hg temperature of 101 F heart rate of 150 per minute and respiration of 40 per minute He was pale and dyspneic The heart was mildly enlarged a summa tion gallop was present and a loud high frequency continuous murmur was heard over the entire precordium

The ECG showed borderline LVH and diffuse changes consistent with acute pericarditis An aortic root and left ventricular angiogram on July 21 1972 revealed a shunt from the left anterior descending (LAD) coronary artery to the right ventricle (RV) an intact ventricular septum and normal great vessels The hemothorax was treated by closed thora ostomy drainage and heroin withdrawal was begun No symptoms ensued from the fistula The murmur persisted and the ECG evolved antero-lateral ischemic changes Cardiac catheterization on August 1 197 showed a negligible RV O_2 stepup and a mildly elevated LVEDP Selective coronary angiography demonstrated a large LAD to RV shunt with d minished LAD flow distal to the fi tula (Fig 1) Because of persisting ischemia and suspected impending infarction surgical correction of the coronary artery steal was performed on August 6 1972 An entrance wound was observed just beneath the LAD about 4 cm from its origin the myocardial wound of exit was on the diaphragmatic

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view of the absence of any demonstrable mural or occlusive disease of other vessels In Case 1, one could argue that the earliest branches of the left coronary, in fact, represent a diminutive circumflex system in a patient with a massively right dominant system Ninety per cent of patients will have this distribution of vessels,[1 5] but most often a well defined circumflex vessel enters the atrioventricular groove In the cases reviewed by James[5] only 1 per cent of the vessels terminated before the crux In our patient the posteroanterior projection of this vessel is atypical for a circumflex artery (Fig 4A and B) Further, the initial branch in question when viewed in motion, moves synchronously with all other branches of the left anterior descending, confirming its lateral course Again none of the vessels visualized shows any evidence of disease so that the likelihood of a totally occluded vessel is slight, at best

Selective metabolic studies sampling the coronary sinus were not performed there fore, we are unable strictly to exclude the possibility of myocardial ischemia

Patient M M (Case 1) had a history of hospitalization for psychoneurosis 10 years prior to his cardiac evaluation Since coronary arteriography, his pain has markedly diminished without the use of cardiac medications His physical activities are unrestricted

Patient D M (Case 2) has continued to have precordial pain, but there has never been electrocardiographic confirmation of ischemia His daily activities have been voluntarily curtailed to exclude excessive exertion

We believe, therefore that the angiograms in these two cases represent congenital absence of the circumflex artery associated with no specifically abnormal electrocardiographic pattern

Summary

Two patients found to have congenital absence of the circumflex coronary artery are reported The clinical electrocardiographic, vectorcardiographic, and cine angiographic findings are presented No distinctive clinical or laboratory abnormalities were found except for the unusual anatomical posterior origin of the ostium of the main left coronary artery

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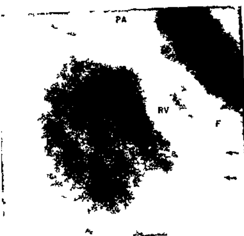


Fig 1 Selective injection of the left coronary artery hows the dilated LAD coronary artery (*arrows*) the site of the fi tula (*F*) and flow of dye through the fistula into the RV The angiogram al o docu ments a coronary steal with markedly dimin ished flow into the distal LAD



Fig 2 Operative photograph showing the site of the fi tula in the back wall of the LAD which has been opened on its anter or urface Proximal and di tal control of the LAD and a large dia onal branch has been obtained by elastomer tapes The entire heart is edematous

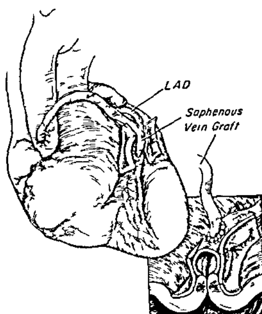


Fig 3 Diagrammatic representation of the surgical repair of the fistula between the LAD coronary ar tery and the RV The fistula in the back wall of the LAD was closed by using mattress sutures placed behind the LAD These sutures were buttressed by strips of Teflon felt Flow to the distal LAD was assured by a complementary saphenous vein bypass graft inserted into the LAD just beyond the fistula

present or detected at the time of initial injury and in several were not manifest until years later Again as illustrated by our case symptoms were frequently not related to the fistula In most patients a hemothorax was present and several were admitted in overt shock In all instances initial wound recovery was uneventful

Acute myocardial infarction was present in five cases and ours and one other had changes of acute myocardial ischemia These changes were in the distribution of the involved coronary artery Patients may be asymptomatic or have minimal symp toms related to these fistulas as in two patients followed for 9 and 20 years In one case however progressive congestive heart failure necessitated surgery after eight months in two others angina pectoris devel oped after 4 and 12 years necessitating surgery and in a third ischemia with exercise led to correction after three years Eight cases had operative correction rang ing from three weeks to 12 years after injury The indication cited most fre quently was a dilated or enlarging coronary artery proximal to the fistula with concern for aneurysm progression or rupture Since pericarditis is a frequent accompaniment of these lesions along with actual myocar dial trauma ECC and enzyme measure ments may be unreliable in assessing the

Table I. Traumatic coronary artery fistulas reported in the literature

Case	Source	Age (yr)	Type of wound	Site of fistula	Management	Results and follow-up
1	Parmley 1958	20	Shrapnel	RC to RA	Observation	Mild dyspnea with exertion after 20 years
	Bravo 1971 (20-year follow up)					
	Jaffee 1973					
2	Jones 1965	18	Gunshot	RC to RA and RV	Surgery after 4 months	Murmur recurred 3 weeks after surgery; patient asymptomatic after 3 months
3	Tsagaris 1966	33	Shrapnel	RC to RA	Surgery after 12 years	Murmur recurred one day after surgery and re-operated
4	Storey 1967	17	Gunshot	RC to RA	Surgery after 9 years	Asymptomatic after 7 years
5	Sarot 1968	30	Stab wound	RC to right coronary vein to RA	Surgery after 4 months	Murmur recurred within hours of surgery and re-operated; asymptomatic after 2 years
6	North 1971	19	Gunshot	RC to RA	Surgery after 6 months	Asymptomatic
7	Lynn 1971	21	Contusion from auto accident	RC to RV	Surgery after 8 months	Murmur recurred after 6 weeks and re-operated; normal examination after 5 years
8	Morgan 1972	17	Contusion from auto accident	LAD to RV	Surgery after 3 years	Murmur recurred after 3 months
	Kahn 1967 (2 year follow up)					
	Forker 1971 (6-year follow up)					
9	Constantino 1972	37	Gunshot	LAD to RV	Observation	Asymptomatic
10	Tsung 1973	38	Stab wound	LAD to LV	Surgery after 4 years	Apical pansystolic murmur of undetermined etiology after surgery; asymptomatic

surface of the RV. The region of the LAD was markedly edematous and the myocardium of the anterolateral aspect of the left ventricle was soft and boggy. A continuous thrill was palpable over the dilated proximal LAD. With the aid of cardiopulmonary bypass, a 4 mm. tear in the posterior surface of the LAD was exposed by a longitudinal arteriotomy in the LAD. This opening communicated via a fistulous channel to the RV near the origin of its outflow (Fig. 2). The LAD and adjacent fistula were undersewn with silk mattress sutures buttressed by strips of Teflon felt. A saphenous vein bypass graft from the aorta to the distal LAD was placed to insure adequate circulation to the anterolateral left ventricular wall (Fig. 3).

The patient recovered uneventfully, but on the fifth postoperative day a similar but softer continuous precordial murmur was again heard. A repeat coronary angiogram on August 16, 1972, revealed a patent bypass graft and LAD, and a diminutive shunt from the LAD to the RV at the site of the initial fistula. Postoperative ECG's showed only nonspecific ST-T wave changes. It was decided not to attempt further correction of the persisting small shunt. When seen in follow-up after six months, the patient was entirely asymptomatic. Physical examination revealed only a Grade 1/VI ejection systolic murmur and the ECG was normal.

Discussion

Although congenital coronary artery fistulas are not uncommon, fistulas secondary to trauma are rare. The present case brings the total number reported to eleven. It also illustrates the remarkable homogeneity of this entity. The mean age of the reported cases is 25 years. Four were caused by bullet wounds, two by contusion incurred in automobile accidents, two by shrapnel, and two by knife wounds. Right coronary (RC) to right atrial (RA) fistulas were most frequent. Our case and two others had LAD to RV shunts and one had an LAD to left ventricular (LV) communication. Aside from the fistulas, two cases had RA lacerations which required immediate repair, one had an LV laceration, one had a VSD, and one a torn tricuspid leaflet. Otherwise, associated cardiac damage was minimal.

Loud continuous precordial murmurs were the hallmark of these lesions. As in the present case, murmurs were not always

seven cases with unusual features Am J Cardiol 3 432 1972

12 Jaffee, R. B Glancy L Epstein S E Brown B G and Morrow A G Coronary arterial right heart fistulae. Long term observations in seven patients Circulation 47 133 1973

13 Constantino T Falcone M W Perloff J K Deleon A C Jr and Jamison W L Traumatic coronary arterial right ventricular fistula Report of a case Med Ann D C 41:70 1972

14 Cheng T O and Adkins P C Traumatic aneurysm of left anterior descending coronary artery with fistulous opening into left ventricle and left ventricular aneurysm after stab wound of chest Report of case with successful surgical repair Am J Cardiol 31 384 1973

presence of myocardial ischemia In our case, the primary indication for surgery was correction of the angiocardiographically demonstrated coronary steal phenomenon relief of distal ischemia evidenced by diminished LAD blood flow, and prevention of actual infarction The present case was the only one in which a saphenous vein bypass was used Follow up is too short to evaluate prevention of infarction but the frankly ischemic preoperative electrocardiogram reverted to only nonspecific changes at the time of hospital discharge and was normal at six months Endocarditis was an additional concern, particularly with the associated heroin addiction In none of the reported cases however, even those with very long intervals prior to correction, was endocarditis reported although this may be due to prophylaxis in some In five corrected patients, the continuous murmur recurred after surgery and required a second operation and in one other a new pansystolic murmur of undetermined etiology was reported In the present case the recurrent shunt was so small that repeat closure was not recommended The frequency of recurrence highlights some of the surgical difficulties Early correction unless necessitated by acute circumstances or, as in our case to prevent potential infarction, should best be delayed to allow subsidence of edema and swelling thereby permitting better surgical delineation correction, and healing It is likely in our case that recurrence of the fistula was due either to opening of a covert channel as myocardial edema resolved or development of a new fistula secondary to postoperative tissue necrosis The reported patients show recurrence developing up to three months after surgery Most reported corrections were remote in time from the initial injury so inadequate healing is not the only factor redissection and adjacent tissue breakdown probably play some role in recurrence

In the absence of specific symptoms or circumstances necessitating surgery, it is not clear that correction is indicated One patient not operated on has been followed for more than 20 years with only mild dyspnea on exertion A recent study of coronary fistulas[11] including one secondary to trauma (Case 1) concluded that there is little anatomic or functional change associated with uncorrected lesions with small or moderate sized shunts after 17 year follow up, but that large shunts probably warrant closure

Cardiac catheterization generally confirmed the diagnosis in the cases reported although as shown by our case the O_2 stepup may be small and insignificant Selective coronary angiography is clearly the procedure of choice for diagnosis and delineation of these lesions

In summary a case of traumatic coronary artery fistula is presented Ten other cases reported in the literature were reviewed and the remarkable homogeneity of this entity was noted The pertinent management problems including pre and post operative course presentation, complications indications for correction and follow up were discussed

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Clinical pathologic conference

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PROFESSOR HEATH A retired window cleaner aged 65 years was seen in Surgical Outpatients on September 14th 1972, with a history of anorexia and epigastric pain of one year s duration The epigastric pain was not related to eating and at times lasted all day He had lost weight for six weeks and had recently started vomiting He had been seen at the hospital in March 1967 with a reducible right inguinal hernia which had been surgically repaired in May 1967 but which had recurred On examination in the Outpatients Department no abnormal physical signs were found but a barium meal was carried out on September 21st He was subsequently admitted to hospital on September 25th No abnormal physical signs were elicited *In particular no ab*normalities were found in the chest the apex beat being felt in the fifth left intercostal space in the mid clavicular line No murmurs were heard The systemic blood pressure was 110/60 mm Hg and the radial pulse was 84 per minute An operation was performed on September 27

Three days after the operation he had a sudden attack of pain in the left hand On examination the left hand and forearm were blue and cold and their power was reduced There was loss of sensation to pin prick over all the fingers and there was blunting to pin prick from the level of the transverse palmar crease to 3 cm below the elbow The brachial and radial pulses were not palpable The patient was not in atrial fibrillation and the radial pulse was regular A few hours after this episode a second operation was performed

One day later on October 2nd the patient was walking to the toilet when he developed a sudden onset of breathlessness and sudden pain in his left loin He looked grey and his systemic blood pressure was 90/60 mm Hg His radial pulse was 110 per minute There was no blood in the urine His respiratory rate was 60 per minute There were rhonchi in the chest and there were basal crepitations There were no abnormal clinical signs in the abdomen *There was no sign of external* hemorrhage His legs were not swollen and the calves were not tender

During the next three to four days he developed urinary retention for which he required catheterization It was noticed that his left leg was becoming swollen and edematous

On October 9th he had a further episode of breathlessness accompanied by cyanosis and sweating On examination he had basal crepitations *Despite treatment* his condition gradually deteriorated and he died on October 14th

Investigations The levels of hemoglobin

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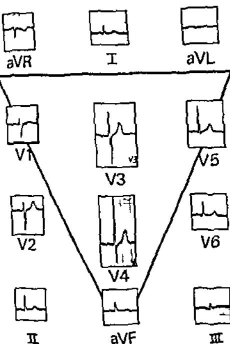


Fig. 1 Electrocardiogram of patient taken on September 26 1972

(Gm per 100 ml) packed cell volume (per cent) and mean corpuscular hemoglobin concentration (per cent) were as follows on May 11 1967 14 9 Gm % 44% 34% on September 26 1972 14 8 Gm % 44% 33% on October 10 1972 11 1 Gm % 35% 32%

The serum creatine kinase level on October 2 1972 was 760 mI U/ml (normal range in our laboratory was 0 to 130) The α hydroxybutyric dehydrogenase level on the same day was 430 mI U/ml (normal range in our laboratory was 153 to 324) Blood group A Rh+

Urine examination on October 2 showed no evidence of hematuria albuminuria or glycosuria

DR SOMERVILLE I have been told that the diagnosis of the case under discussion today requires clinical acumen If a woman is right under these circumstances it is called intuition but if a man is right it is knowledge! Our patient had a year s history of anorexia and epigastric pain which eventually became associated with vomiting I do not believe that his inguinal hernia is relevant because within six days of having a barium meal examination he



Fig 2 Radiograph of patient s chest taken on September 26 1972

was on the operating table Clearly this man had an acute severe and possibly malignant condition I think it likely that he had a carcinoma of the stomach

MR BREWER That diagnosis was supported by the results of the barium meal examination which showed destruction of the normal antral mucosa and gross deformity of the pre pyloric region of the stomach with some degree of stenosis

DR KHALIQ Later at necropsy it was confirmed that there was an ulcerating annular carcinoma 5 cm in extent in the grossly narrowed pyloric canal Histological examination showed an adenocarcinoma of the stomach which had penetrated the full thickness of the muscle coat and metastasized to one regional lymph node

MR BREWER A gastroenterostomy was carried out

DR SOMERVILLE I note that at the time of the operation there were no abnormal signs in the chest Furthermore the chest radiographs and electrocardiograms taken in 1967 and 1972 were normal (Figs 1 and 2) Three days after operation he had a sudden attack of pain in the left forearm and hand which were blue and cold and suffered loss of power and sensation The brachial and radial pulses were not palpable That adds up to only one thing a sudden arterial occlusion There are rela

tively few causes of sudden occlusion of this type He may have had a dissecting aneurysm, but in my experience this would almost certainly be associated with central chest pain if it involved the left subclavian artery and it would not present just as pain in the hand He is more likely to have had an embolus, and presumably the second operation reported was an embolectomy Since the brachial and radial pulses were not palpable the embolus must have been above that level and presumably was in the axillary artery

Such emboli can arise from various sites They may originate from thrombus in the left atrium or left atrial appendage Thrombosis arising there is usually associated with a change of rhythm, usually atrial fibrillation This did not apply to the patient under discussion although it is possible that he may have had a short paroxysm of fibrillation before he was seen by a doctor or nurse Sometimes patients with mitral stenosis do throw off emboli into the systemic arteries without atrial fibrillation, but I am inclined to think that in a man of 65 years with mitral stenosis atrial fibrillation would have been present Another source of embolism in the left atrium is a myxoma but of course in this case the surgeons would have detected fragments of myxoma and not thrombus from the brachial artery

MR RAWSTHORNE At the second operation the brachial artery was approached medially and the material removed was recent thromboembolus it did not resemble the jelly like appearance of myxoma

DR SOMERVILLE However you would agree that fragments of myxoma can have recent thrombus superimposed on them disguising their true nature Another source of embolus is mural thrombus following infarction of the left ventricle, but there is no evidence of that and I would discard that diagnosis I notice the elevated enzymes but I presume this is related to the death of muscle following arterial embolism in the arm Thrombus too can arise over atheromatous plaques on the aorta

DR ROBERTSON Would you expect to find a myxoma of the left atrium or trivial mitral stenosis in a man of 65 years with a heart of normal size?

DR SOMERVILLE Yes, I believe it is possible to have a small myxoma which does not cause physical signs and recent thrombosis on such a small mass might lead to systemic embolism We might be helped in this diagnosis by finding a raised sedimentation rate or abnormalities in the plasma proteins With regard to mitral valve disease, I do believe one can find trivial mitral stenosis in the elderly not leading to cardiac enlargement

PROFESSOR HEATH Perhaps at this point I could summarize the argument so far by saying that we are seeking a source of systemic emboli occurring in a man with no clinical, electrocardiographic or radiological evidence of cardiopulmonary disease

DR SOMERVILLE That is right This is a practical problem that the Cardiologist comes across from time to time Another possibility at the back of my mind is the situation where one may have a small atrial septal defect with a paradoxical embolus from the venous site However, I do not favor this diagnosis in view of the normal chest radiograph and electrocardiogram It seems more likely to me that we are dealing with an embolus which has arisen from the left ventricle or systemic arteries

Two days after the embolectomy the patient developed breathlessness, an increase in respiratory rate and a fall in systemic blood pressure It seems likely that he had a pulmonary embolus I notice that at this stage they found no evidence of thrombosis in the deep veins in the leg, but of course this does not necessarily exclude a pulmonary embolus because the first may occur without such clinical signs in the leg It is also conceivable that he had a hemorrhage The hemoglobin level fell during this period, but of course this is confused by the fact that he had a recent operation The pain he experienced in the left loin could also have been produced by a renal or splenic infarct As there was no hematuria I favor the latter diagnosis

PROFESSOR HEATH Perhaps you would like to look at the next slide which shows a picture of the man s legs as they appeared in the terminal phase of his illness

DR SOMERVILLE Were arterial pulses present in the left leg?



Fig 3 View of the heart from its superior aspect The roof of the atria and the upper portion of the interatrial septum have been removed A large thromboembolus (*E*) is impacted in an atrial septal defect which lies immediately beneath the rim of alveolar septum indicated by the arrow While most of the thromboembolus (*E*) lies in the right atrium (*RA*) a small part lies in the left atrium (*LA*) (Original magnification ×1 3)

MR RAWSTHORNE Yes the pulses were full

DR SOMERVILLE Well in that case I believe the cause of the swelling in that leg was a deep venous thrombosis rather than an arterial embolism

PROFESSOR HEATH Well in that case how do you fit together all the changes you have been describing? You consider that we are dealing with a deep vein thrombosis in the left leg associated with pulmonary embolism There is systemic arterial embolism in the left arm and you describe the possibility of a splenic infarction How do you relate all these things together?

DR HENDERSON Do you think that all these signs and symptoms described could be explained on the basis of *thrombophlebitis migrans?*

DR HARLEY Do you think it likely that the source of the emboli was thrombosis in the pulmonary veins?

DR SOMERVILLE I have seen tumor in pulmonary veins following extension from a bronchial carcinoma which has given rise to systemic embolism but of course we have no evidence of a tumor of lung in this case

MR POPE You say that there could not have been an atrial septal defect because it would have shown up on the radiograph or electrocardiogram but would this apply to very small defects?

DR SOMERVILLE At this age the most likely type of atrial septal defect that would allow an embolus to pass from systemic veins into systemic arteries would be a defect of secundum type but by this age of 65 years I would have anticipated that the heart would be enlarged Furthermore I would have anticipated some evidence of right ventricular hypertrophy in the electrocardiogram Of course one does have to bear in mind that an embolus might pass through a small valvar foramen ovale that had never given rise to symptoms or which did not reveal itself on clinical radiographic or electrocardiographic examination However this would have been unlikely to occur unless there was some increase in pressure in the right atrium and there does not appear to be any basis for this

MR SHATWELL Surely such a rise in pressure might have been produced by the



Fig 4 View of the heart from the left atrium (*LA*) after removal of the main portion of thromboembolus The atrial septum has been cut along the line indicated by the black arrows An atrial septal defect (*white arrow*) communicates with the right atrium (*RA*) Thromboembolus (*E*) is still impacted in a persistent valvar foramen ovale (Original magnification ×2 5)

thromboembolism to the lung which you consider occurred?

DR SOMERVILLE Yes it could However, the emboli to the brachial artery occurred before evidence for the possible pulmonary embolism

DR KAY Surely pulmonary emboli can be silent?

DR SOMERVILLE I agree but since only five days elapsed between the time of operation and the impaction of the embolus in the left arm, one would have to postulate a lot of silent pulmonary emboli in that time to raise the pressure in the right side of the heart

PROFESSOR HEATH I think at this stage we could ask Dr Khaliq what he found at necropsy

DR KHALIQ The body was that of an elderly man of medium build and short stature (5 ft 5 in) Partially healed gastroenterostomy and embolectomy wounds were present The left lower limb was swollen and edematous due to thrombosis of the left femoral vein There was bilateral pulmonary thromboembolism Emboli of various ages were found occluding lobar and segmental branches of both main pulmonary arteries On histological examination some of these emboli were partially organized Some had blocked muscular pulmonary arteries and hence appeared to have been capable of elevating pulmonary vascular resistance The heart was dilated and weighed 466 Gm (with attached fat) There was an elongated thromboembolus in the right atrium which was 6 cm in length and 2 5 cm in diameter It was impacted in a small atrial septal defect and protruded into the left atrium (Fig 3) The atrial septal defect was 1 cm in diameter anterior to the fossa ovalis and had a crescentic upper border with no septal tissue at the lower border (Fig 4) A smaller embolus (0 4 cm in diameter) was impacted in a persistent foramen ovale Both coronary arteries were patent and showed minimal non occlusive atheroma The myocardium was normal The mitral tricuspid aortic, and pulmonary valves were normal

The right ventricle was very dilated

The liver was congested and sections showed centrilobular venous congestion. The spleen had a wedge shaped infarct at its lateral margin. The urinary bladder was hypertrophied due to prostatic enlargement due to benign fibroleiomyoepithelial hyperplasia

This was a case of paradoxical embolism in which emboli arising from thrombi in the left femoral vein reached the peripheral systemic arterial circulation through defects in the atrial septum. Repeated thromboemboli also reached the lung elevating pulmonary vascular resistance and the pressure in the right atrium. This would have favored the passage of thromboemboli through the atrial septal defect and the persistent foramen ovale. The defects in the atrial septum themselves became occluded by impaction of thromboemboli. The passage of emboli through these defects or fragmentation of the impacted emboli would account for the episodes of systemic arterial embolism occluding the left brachial artery and leading to infarction of the spleen

PROFESSOR HEATH As a pathologist one has to say that paradoxical embolism is one of those classical conditions that one includes in undergraduate teaching and yet rarely sees. It is described in most textbooks of pathology but how common is this condition?

DR SOMERVILLE I think it is seen very rarely in clinical practice but one does have to say that it occurs in the very type of case we have been discussing today where there is a small atrial septal defect. I have previously seen two cases of paradoxical embolism both occurring in elderly patients with deep vein thrombosis and small atrial septal defects. I think this is fascinating and certainly the pathologist has been able to explain all the signs and symptoms here on the basis of one pathology as he so frequently can but of course he has rather a selected referral of patients! However I still think that the first event in this patient was a systemic arterial embolism. At that stage there was no evidence that he had had previous pulmonary embolism

PROFESSOR HEATH Rare as this condition is it would appear to be even rarer to actually catch an embolus in the process of impaction and passage through the foramen ovale. What about the incidence of paradoxical embolism in congenital heart disease such as a ventricular septal defect or a patent ductus arteriosus?

DR SOMERVILLE This is not likely to occur because the flow of blood through such defects is in the wrong direction for it to happen namely from left to right. In the presence of pulmonary hypertension with reversal of flow it could occur. In an atrial septal defect there is part of the cardiac cycle where it is quite easy for reversal of flow of blood to take place. During atrial diastole the pressure in the right atrium may be slightly higher than in the left thus allowing a right to left shunt and then one could of course have a paradoxical embolus. I am interested in the description of the atrial septal defect. Small ostium primum defects are not necessarily associated with the characteristic electrocardiographic changes. However I would have expected some abnormality in the anterior cusp of the mitral valve

PROFESSOR HAY I don't remember seeing cases of paradoxical embolism in congenital heart disease. How often do you get an atrial septal defect of that size with a normal electrocardiogram?

DR SOMERVILLE Well I think there is no doubt that unsuspected patency of the atrial septum is found not infrequently at necropsy. It is clear from this meeting today that such patency can lead very rarely to paradoxical embolism. If this man had not had the carcinoma and associated deep vein thrombosis it seems very unlikely that his small atrial septal defect would have caused him any trouble at all or perhaps even come to light

DIAGNOSIS Paradoxical embolism
Atrial septal defect
Carcinoma of stomach

Fundamentals of clinical cardiology

Straight back syndrome

Clinical and hemodynamic study of 9 cases

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Rawlings[1] first described the straight back syndrome as a cause of pseudo heart disease in 1960, and additional reports have followed.[2-5] We have studied 9 cases of straight back syndrome, finding a small systolic pressure gradient between the right and main pulmonary arteries in one catheterized case. The purpose of this paper is to describe the clinical and hemodynamic findings of these 9 cases and to discuss in detail the one having the pulmonary arterial pressure gradient.

Material and methods

Nine patients (4 males and 5 females) with straight back syndrome were studied between January, 1964, and April, 1968, in the First Department of Internal Medicine, Nagasaki University School of Medicine, Japan. Ages ranged from 12 to 18 years (average 15.6 years). Two patients were referred with the diagnosis of atrial septal defect (Cases 5 and 8). The others were referred for evaluation of cardiac murmurs. The criteria used for patient selection were a straight thoracic spine on inspection and a lateral chest x-ray. A complete history and physical examination as well as electrocardiograms (ECG's) and phonocardiograms (PCG's) were obtained. In each patient, the ratio of the anteroposterior dimension to the transthoracic dimension was calculated from the chest x-ray as described by De Leon and associates.[5] Right heart catheterization was performed in 6 patients, including right-sided angiocardiography in 4.

Results

The physical, chest roentgenographic, ECG, and PCG findings are summarized in Table I. All patients had absence of the normal kyphotic curvature of the thoracic spine on inspection (Fig. 1). Two patients also had mild pectus excavatum (Cases 5 and 8, Table I). On physical examination, all patients had a systolic ejection murmur, Grade 2-3/6 in intensity, at the pulmonary area. Splitting of the second sound was observed in all cases, varying from 0.03 to 0.06 sec. on expiration and increasing with inspiration. There were no other notable physical findings. PCG recorded in the second intercostal space at the left sternal

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Table I The physical chest roentgenographic PCG and ECG findings in 9 patients with straight back syndrome

Patient no	Initials age and sex	Straight back	Pectus excavatum	Chest x-ray				PCG		ECG		
				Prominence of PA	Left sided shift	Pancake appearance	AP / transthoracic ratio	Syst mur	Split of S_2	RAD	rSr in V_1	Clockwise rotation
1	Y O 12 F	+	−	+	−	+	30%	+	+	+	−	−
2	M T 13 M	+	−	−	−	+	35%	+	+	−	+	−
3	N K 14 F	+	−	+	−	+	[illegible]%	+	+	+	+	+
4	H N 16 F	+	−	+	+	+	33%	+	+	−	−	−
5	S S 16 F	+	+	+	−	−	35%	+	+	−	−	−
6	M K 17 F	+	−	+	−	−	3[illegible]%	+	+	+	−	−
7	H K 17 M	+	−	+	−	−	35%	+	+	−	−	+
8	T I 17 M	+	+	+	−	−	3[illegible]%	+	+	−	+	+
9	Y T 18 M	+	−	+	−	−	35%	+	+	+	−	−

Abbreviations M = male F = female PA = pulmonary artery AP/transthoracic ratio = anteroposterior diameter/transthoracic diameter ratio PCG = phonocardiogram Syst mur = systolic murmur at the pulmonary area Split of S_2 = splitting of the second sound ECG = electrocardiogram RAD = right axis deviation

border are shown in Fig 2 The ECG findings were an axis varying from 90 to 110 degrees in 4 patients and an rSr pattern (r ≧ r) in V_1 and V_{3R} in two other patients (Fig 3) One additional patient had both of these findings Chest x ray revealed prominence of the pulmonary artery conus in 8 patients (Fig 4) and left sided shift of the heart shadow in one patient (Fig 5) There was a pancake appearance of the heart in 4 patients (Figs 4 and 5) The ratio of the anteroposterior diameter to the transthoracic diameter varied from 27 per cent to 37 per cent These ratios are decreased below normal in all except one case (Case 6)

A summary of the right heart catheterization data in 6 patients including angiocardiography in 4 is shown in Table II A slight increase in right ventricular systolic pressure (> 30 mm Hg) was observed in 3 patients Five patients had a small resting systolic pressure gradient (4 to 13 mm Hg) across the right ventricular outflow tract No cases showed arteriovenous shunting Angiocardiography was performed in 4 patients Three of these showed flattening of the right ventricular outflow tract (Fig 6) and two showed compression of the anterior wall of the right ventricle against the sternum (Fig 7)



Fig 1 View of the posterior thorax in Case 3 The dorsal spine lacks the normal outward curve

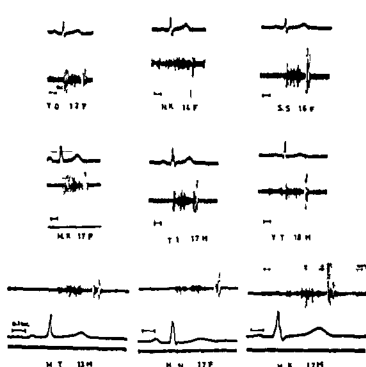


Fig 2 Phonocardiogram of all 9 cases All are recorded at the left sternal border in the second intercostal space on expiration

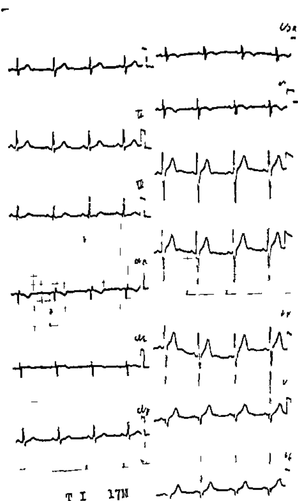


Fig 3 Electrocardiogram in Case 8

In Case 1 although there was no clear stenosis of the main right pulmonary artery on angiocardiography an abrupt systolic pressure gradient of 10 mm Hg was observed in the main right pulmonary artery as the catheter was withdrawn from the peripheral right pulmonary artery to the main pulmonary artery (point A to point B Fig 7) This pressure change was recorded where the right pulmonary artery passed anteriorly to the straight thoracic spine This maneuver was performed three times (Fig 8) with identical results

Discussion

Straight back syndrome is sometimes misdiagnosed as organic heart disease most frequently atrial septal defect idiopathic pulmonary artery dilatation or mild pulmonary stenosis[1,2,5] Two of our cases (Cases 5 and 8) were thought to have atrial septal defect because of the findings of a wide splitting of the second sound and an ejection systolic murmur in the pulmonic area prominence of the pulmonary conus on the chest x ray film and an rSr′ pattern in Leads V_1 and V_{3R} of the ECG

All but one of our cases showed prominence of the pulmonary artery segment on chest x ray This finding as well as the leftward shift and pancake appearance t e



Fig 4 Anteroposterior chest x ray in Case 1 showing prominence of the pulmonary artery Lateral view shows a straight dorsal spine and narrow anteroposterior diameter with diminished retrocardiac space



Fig 5 Anteroposterior view of the chest x ray in Case 3 showing leftward displacement of the heart and slight prominence of the pulmonary artery Lateral view shows a straight dorsal spine and narrow anteroposterior diameter

heart may be explained by rotation and displacement due to narrow anteroposterior diameter of the thorax in this syndrome In all but one of our cases the ratios of the anteroposterior to transthoracic diameters of the chest x ray were under 37 per cent significantly less than the values described as normal by De Leon and associates[9] These investigators suggested that the systolic murmur in the second left intercostal space may relate both to displacement of the main pulmonary artery and to an exaggeration of the normal ejection vibration due to the proximity of the vessel to the chest wall

In this regard angiocardiographic study showed compression of the right ventricle and proximity of the pulmonary artery to the chest wall in two cases (Fig 7) and flattening of the outflow tract of the right ventricle in three cases (Fig 6)

Association of pectus excavatum with the straight back syndrome was reported in one of twelve cases by Rawlings[2] and two

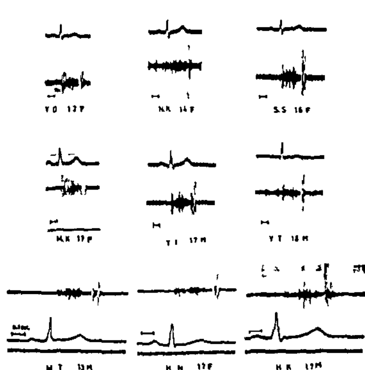


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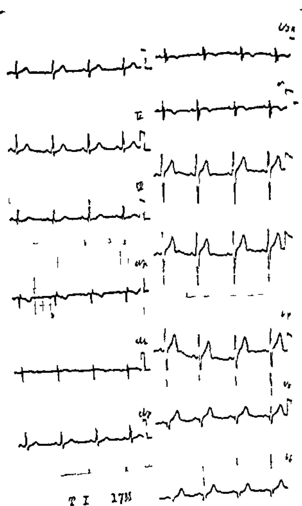


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All but one of our cases showed prominence of the pulmonary artery segment on chest x ray This finding as well as the leftward shift and pancake appearance of the



Fig 7 Anteroposterior (*left*) and lateral view (*right*) of the right ventricular angiogram in Case 1 The anterior wall of the right ventricle is compressed against the sternum in the lateral view

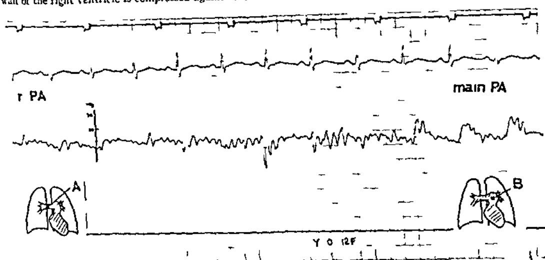


Fig 8 Continuous pressure tracing as the catheter was withdrawn from point A in the right pulmonary artery to point B in the main pulmonary artery (Case 1) *A* and *B* correspond to the same points on the angiogram in Fig 7

catheter tip did not appear to be wedged on fluoroscopy and the difference in pressure occurred in the main branch of the right pulmonary artery when the catheter was continuously withdrawn from a peripheral pulmonary artery Small systolic pressure gradients between the pulmonary branches and main pulmonary artery may be functional in conditions with large pulmonary blood flow due to left to right shunt[14] However this patient had no arteriovenous shunt by blood oxygen studies or on angiocardiography Although mild congenital pulmonary artery stenosis[9, 11, 15] cannot be excluded as a cause of the pressure gradient we believe that compression of the right main pulmonary artery as it crosses the straight thoracic spine better explains the gradient in this case Leinbach and co workers[8] have reported one case of straight back syndrome with pulmonary venous obstruction They concluded that this was due to sternospinal cardiac compression

This brief report also serves to re emphasize a clinically recognizable entity which



Fig 6 Anteroposterior (*left*) and lateral view (*right*) of the right ventricular angiogram in Case 8 The flattening of the right ventricular outflow tract is seen in the lateral view

Table II Right heart catheterization data in 6 patients, including angiocardiography in 4 patients

Patient initials age, and sex	*RA (mm Hg)*			*RV (mm Hg)*	*PA (mm Hg)*	*L R shunt*	*ACG*		
	a	*v*	*mean*				*PA valv stenosis*	*Flat of RV outlet*	*Comp of ant wall of RV*
Y O 12 F	7	7	4	28/0-7	mPA 24/8 rPA 14/7	−	−	+	+
N K, 14 F	5	5	4	30/0-5	26/10	−	−	±	−
S S 16 F	7	5	4	30/0-7	30/10	−	−	+	+
M K 17 F	6	5	4	35/0-4	28/10	−			
T I 17 M	5	4	3	38/0-4	25/10	−	−	+	−
Y T 18, M	5	5	3	38/0-5	25/8	−			

Abbreviations RA = right atrium RV = right ventricle PA = pulmonary artery L R shunt = left to right shunt mPA = main pulmonary artery rPA = right pulmonary artery PA valv stenosis = pulmonary valvular stenosis Flat of RV outlet = flattening of the right ventricular outflow tract Comp of ant wall of RV = compression of the anterior wall of the right ventricle against the sternum ACG = angiocardiography

of 23 cases by Gooch and colleagues[7] In the present study, two of nine cases had associated mild excavatum

In Case 1, although there was no clear narrowing of the right pulmonary artery on the angiocardiogram a mild abrupt systolic pressure gradient was observed on pressure recording when the catheter was pulled back from the peripheral right pulmonary artery to the main pulmonary artery This gradient occurred at the point where the right main pulmonary artery crossed in front of the straight thoracic spine (Fig 8) To our knowledge there has been no previous report of such a finding in association with this syndrome

Baum and associates[9] found false pressure gradients in the pulmonary arteries could result from (1) wedging of the catheter tip in a small pulmonary artery branch (2) partial obstruction of the flow of blood by the catheter in the artery catheterized and (3) the small, though normal differences in pressure that may be found in various regions of an anatomically normal pulmonary artery system In the present case the

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Therapeutic uses of atrial pacing

Seymour Furman M D
Bronx N Y

Ventricular cardiac pacing has a secure well-established and well-delineated place in the treatment of heart disease and cardiac arrhythmias Atrial pacing to the contrary is irregularly used and with a slowly evolving group of indications The reasons for the difference are

1 The difficulty in establishing consistent atrial pacing and sensing[1]

2 The paucity of atrial or ventricular arrhythmias controllable by atrial pacing relative to those amenable to ventricular pacing and the realization that the effects of atrial arrhythmia usually can be ameliorated or adequately treated by the more readily applied stable and reliable ventricular pacing

3 The presence almost everywhere in the heart of a ventricular signal at least as large and frequently much larger than the atrial signal so that pacemaker triggering from the atrial signal alone may be erratic and sensing from either the atrial or the ventricular signal or both may occur[2] Atrial activity can fail to recycle an atrial pacemaker or it can be recycled by a QRS complex effectively slowing the rate of atrial stimulation

4 The existence of intermittent or partial atrioventricular block so that the ventricle may not at all times be affected by atrial pacing sometimes when the circumstances most require[3]

5 The late development of atrial fibrillation or flutter which negates the effect of atrial pacing on the ventricle

Nevertheless indications for atrial pacing exist in which stimulation of the atria is an excellent alternative to ventricular pacing[4] and others for which atrial pacing is to be preferred to ventricular pacing[5]

The major therapeutic indications for atrial pacing are

- I Bradycardia caused by an inadequate sinus or atrial rate in the presence of intact atrioventricular conduction
  - A Episodic sinus bradycardia sinus arrest or sinoatrial block with asystole
  - B As above with periods of supraventricular tachycardia—i e the bradytachy syndrome
- II Suppression of ventricular irritability by an overriding conducted atrial rhythm
- III Atrioventricular synchrony to increase cardiac output
  - A By direct atrial pacing in the presence of intact A V conduction
  - B By atrio ventricular sequential

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should be borne in mind when certain mild congenital heart lesions are suspected

Summary

Clinical, electrocardiographic, radiologic, and hemodynamic findings in 9 cases of straight back syndrome are described In one case a small systolic pressure gradient was observed as the catheter was pulled back from the peripheral right pulmonary artery to the main pulmonary artery To our knowledge this is the first report of a gradient associated with this syndrome The possible hemodynamic causes are discussed It is re emphasized that the cardiac findings in straight back syndrome frequently mimic those of certain mild congenital heart defects

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Appraısal and reappraısal of cardıac therapy

Edıted by Arthur C DeGraff and Julian Frıeden

Therapeutıc uses of atrıal pacıng

Seymour Furman M D
Bronx N Y

Ventrıcular cardıac pacıng has a secure well-establıshed and well-delıneated place ın the treatment of heart dısease and cardıac arrhythmıas Atrıal pacıng to the contrary ıs ırregularly used and with a slowly evolvıng group of ındıcatıons The reasons for the dıfference are

1 The dıffıculty ın establıshıng consıstent atrıal pacıng and sensıng [1]

2 The paucıty of atrıal or ventrıcular arrhythmıas controllable by atrıal pacıng relatıve to those amenable to ventrıcular pacıng and the realızatıon that the effects of atrıal arrhythmıa usually can be amelıo rated or adequately treated by the more readıly applıed stable and relıable ven trıcular pacıng

3 The presence almost everywhere ın the heart of a ventrıcular sıgnal at least as large and frequently much larger than the atrıal sıgnal so that pacemaker trıg gerıng from the atrıal sıgnal alone may be erratıc and sensıng from eıther the atrıal or the ventrıcular sıgnal or both may occur [2] Atrıal actıvıty can faıl to recycle an atrıal pacemaker or ıt can be recycled by a QRS complex effectıvely slowıng the rate of atrıal stımulatıon

4 The exıstence of ıntermıttent or partıal atrıoventrıcular block so that the ventrıcle may not at all tımes be affected by atrıal pacıng sometımes when the cırcumstances most requıre [3]

5 The late development of atrıal fıbrılla tıon or flutter whıch negates the effect of atrıal pacıng on the ventrıcle

Nevertheless ındıcatıons for atrıal pacıng exıst ın whıch stımulatıon of the atrıa ıs an excellent alternatıve to ventrıcular pacıng[4] and others for whıch atrıal pacıng ıs to be preferred to ventrıcular pacıng [5]

The major therapeutıc ındıcatıons for atrıal pacıng are

- I Bradycardıa caused by an ınade quate sınus or atrıal rate ın the pres ence of ıntact atrıoventrıcular con ductıon
  - A Epısodıc sınus bradycardıa sınus arrest or sınoatrıal block wıth asystole
  - B As above wıth perıods of supra ventrıcular tachycardıa—ı e the bradytachy syndrome
- II Suppressıon of ventrıcular ırrıtabılıty by an overrıdıng conducted atrıal rhythm
- III Atrıoventrıcular synchrony to ın crease cardıac output
  - A By dırect atrıal pacıng ın the presence of ıntact A V conduc tıon
  - B By atrıo ventrıcular sequentıal

F m the Cardıotho acıc Servıce Dı ıo of Su g ry Mo tefıore Hospıtal and Med cal C ter B nx, N Y
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pacing in the presence of A V block
IV Rapid atrial pacing to terminate supraventricular and re entry tachycardias

Physiology of atrial pacing

Atrioventricular synchrony usually produces greater cardiac output than ventricular paced rhythms[6] In the presence of complete heart block atrioventricular asynchrony with lack of the atrial contribution reduces output compared to A V synchrony [7] If conduction is present (ventricular pacing for sinus bradycardia) then retrograde stimulation of the atrium and atrial *contraction during ventricular sys*tole against a closed atrioventricular valve reduces cardiac output even further [8]

In the *normal* however the contribution of atrial systole during right atrial pacing increases cardiac output little compared to direct ventricular pacing [9] Exercise in the normal during atrial or ventricular pacing at similar rates causes similar increases in stroke volume and cardiac output [10]

In those with heart disease unlike the normal, increasing cardiac rates with atrioventricular synchrony usually produces increases in cardiac index, time tension index, ventricular power mean systolic pressure and systolic ejection compared to ventricular pacing at similar cardiac rates [11,12] Exercise in those with cardiac disease produces greater increments in cardiac output with atrial compared to ventricular pacing at similar rates [13]

Atrial pacing requires less ventricular work to produce more rapid ejection time greater left ventricular end diastolic pressure and aortic systolic pressure than ventricular pacing [14] Atrial synchronous pacing and in all likelihood atrioventricular sequential pacing produce cardiac outputs 15 to 20 per cent greater than continuous direct ventricular pacing under these circumstances [15]

After cardiac surgery and acute myocardial infarction maximum cardiac efficiency is required and atrioventricular synchrony at rapid (80 to 100) physiologic rates can produce cardiac outputs up to 60 per cent greater than ventricular pacing at the same rate In the presence of insufficiency of the A V valves especially the mitral, direct ventricular pacing may decrease cardiac output Stroke volume and arterial pressure for a single beat decrease when atrium and ventricle are out of phase and increase when fortuitous synchrony occurs In the presence of A V valvular insufficiency during ventricular pacing the asynchronous ventricular contractions will be associated with reductions of output either for a single or for a succession of several asynchronous beats [16] Reductions of stroke volume may be to 50 per cent of normal levels If block is frequent the total cardiac output drop may be pro*found If it is infrequent the patient may* be almost as symptomatic during periods of apparently normal cardiac pacing as before the pacer was inserted [17]

This event referred to as pacemaker syndrome is most effectively managed by the restoration of A V synchrony [18] In the presence of normal atrial rate and heart block atrial synchronous (atrial triggered ventricular pacing) and in the presence of sinus bradycardia or arrest atrioventricular sequential pacing are both satisfactory solutions to the problem [19] If sinus bradycardia without heart block exists then direct atrial pacing is satisfactory [20] Direct corrective action toward mitral or tricuspid valve may be required

The atrial electrode

Implantation of an atrial electrode by thoracotomy is not difficult and several approaches exist The flat spiral atrial epicardial electrode used as an atrial sensor for atrial synchronous pacing can be used to sense and pace the atrium Electrodes designed for transvenous ventricular *stimu*lation can be adapted for suture to and stimulation of the atrium [21]

The problem of transvenous atrial electrode placement has not been definitively resolved though occasional papers with small successful series appear Ventricular stimulating electrodes may be placed in the coronary sinus from which stable atrial pacing and intermittently satisfactory sensing is possible [22] A J shaped electrode may be placed into the atrial appendage and is also effective for pacing, though less so for

sensing the P wave[24, 25] An electrode with wires projecting (harpoon like) from its tip may be introduced within a larger plastic catheter with a lumen into the atrial appendage[26] The lumen catheter is large and difficult to manipulate and the author has failed to place it in about half the attempts An ingeniously designed electrode introduced from the femoral vein via a modified Ross needle perforates and grasps the atrium septum[27] This approach leaves the connection to a pacemaker in the lower abdomen as the electrode is brought subcutaneously through the groin Connection to a ventricular electrode as well as to the atrial seems difficult should atrial synchronous or A V sequential pacing be desired

Modes of atrial pacing

I *Asynchronous atrial pacing* Stimulation of the atrium is continuous the pacemaker does not respond to atrial or ventricular activity The rhythm is useful as it avoids the problems of sensing spontaneous atrial activity and can best be used when fixed sinus bradycardia with satisfactory A V conduction at least at physiologic rates exists Such pacing can be applied via any of the electrode placement techniques

II *Atrial triggered pacing* Two major subgroups exist These are atrial triggered ventricular pacing commonly referred to as atrial synchronous or P wave triggered pacing which will not be discussed further and atrial triggered (non competitive) atrial pacing

In atrial triggered atrial pacing atrial activity modifies the pacemaker activity in a fashion analogous to the modification of ventricular pacing by ventricular activity

A ATRIAL INHIBITED ATRIAL PACING Stimulation of the atrium occurs if the atrial rate is below the pacemaker escape rate Increase in the spontaneous atrial rate inhibits pacemaker stimulation A relatively conventional pulse generator may be used though its sensitivity should be to a one millivolt signal rather than to the more conventional two millivolt (ventricular) signal

Two problems may arise (1) the increased pulse generator sensitivity may still be inadequate to sense atrial activity and pacemaker competition with atrial activity may occur yielding pacemaker induced premature atrial contractions and (2) the ventricular signal as indicated earlier is large throughout the heart As most inhibited pulse generators have short refractory periods (the longest for widely used generators is 250 msec) the possibility exists that following atrial stimulation the pacer may be inhibited and be recycled by the subsequent QRS complex

B ATRIAL SYNCHRONIZED ATRIAL PACING In this instance a synchronous pulse generator is employed It too should be of one millivolt sensitivity and the same electrode sensing problems exist as for an inhibited pacer However as synchronous pacemakers have a refractory period of 350 to 400 msec it is unlikely that the QRS complex will occur early enough to recycle the pulse generator An additional advantage is that transcutaneous increase of pulse generator rate is readily possible and that atrial rates up to 145 per minute can be imposed[28] if required to override a tachycardia

III *Atrioventricular sequential* When sinus activity is sufficiently slow that increase in atrial rate is desirable but A V conduction is compromised or unreliable pacing is required for both atrium and ventricle especially when the atrial contribution to cardiac output is of great consequence[29] Four circumstances exist

1 Acute myocardial infarction with heart block and sinus bradycardia these patients obviously require the maximum of cardiac efficiency and cardiac output can be increased by the restoration of atrioventricular synchrony compared to direct ventricular pacing[30]

2 Postoperative cardiac surgery the same circumstances exist as following myocardial infarction[31]

3 With more profound degrees of myocardial failure the atrial contribution plays a greater role in cardiac output In severe congestive heart failure a physiologically timed atrial contraction will provide a much greater cardiac output than will asynchronous ventricular pacing (see above)[32]

4 With severe insufficiency of the A V

valves especially the mitral direct ventricular pacing accentuates the degree of insufficiency and cardiac output *may fall* rather than rise with an increase in cardiac rate If the atrial rate is adequate, atrial synchronous pacing will ameliorate the problem, if not A V sequential pacing is required

A V sequential pacing may be at a fixed atrial rate a fixed A V delay and with asynchronous ventricular pacing assuming that no competitive spontaneous ventricular activity will occur A more satisfactory approach especially when the possibility exists either of spontaneous atrial activity with conduction or premature ventricular activity is such pacing with ventricular inhibition an approach called Bifocal demand* (atrioventricular sequential ventricular inhibited) pacing [33]

The Bifocal demand pacer designed both as an external and as an implantable model has at least in its implantable form suffered from serious technical problems which have severely restricted its utility

IV *Rapid atrial pacing* To this point pacing of the atrium has assumed a physiologic rate of stimulation analogous to ventricular pacing at a similar rate A unique approach to atrial pacing is that of rapid stimulation of the atrium at rates of 400 to 1 200 per minute with no attempt to achieve A V conduction [34] The ventricle is protected from such rates by the inability of the conduction system to transmit such rapid impulses The attempt is to convert a pathologic atrial rhythm to regular sinus rhythm [35] Rapid atrial pacing is asynchronous manually applied and terminated Rapid atrial pacing operates in one of three distinct fashions In the presence of an atrial or junctional tachycardia the pacemaker rate may be set above the atrial rate capture and then allow slowing Alternatively a continuous and stable atrial arrhythmia is converted to an unstable rhythm which reverts to regular sinus rhythm and finally circus or reciprocating pathways may be interrupted by the rapid pacemaker stimuli

1 *Atrial flutter* Atrial flutter can frequently be converted to atrial fibrillation or regular sinus rhythm by rapid atrial pacing Wide variability of results exists one report was of success in 48 of 68 attempts with 21 converted to sinus rhythm and 27 to atrial fibrillation of which sixteen ultimately returned to sinus rhythm [36] In another group of 15 patients seven resumed atrial flutter with the cessation of atrial pacing and six remained in atrial fibrillation [37] In the remaining two capture of the atrium never occurred In all direct current cardioversion was eventually required Rapid atrial pacing is a secondary procedure for atrial flutter but may be attempted for its ease of application without the use of anesthesia and in the presence of digitalis intoxication without the danger of ventricular tachy fibrillation [38]

2 *Supraventricular tachycardia* Supraventricular tachycardia both atrial and nodal may not be controlled by overriding atrial pacing within the physiologic range (100 to 180 per minute) [39] Even pacing at a rate in excess of the atrial rate may not capture control and break the tachycardia Rapid atrial pacing converts the tachycardia to atrial fibrillation an unstable rhythm which then often reverts to a regular rhythm Both discrete impulses and 60 Hz alternating current have been used successfully with similar results [40,41]

Increases of atrial rate by rapid atrial pacing may not produce atrial fibrillation but an atrial tachycardia with increasing atrioventricular block—i e 3 1 to 5 1 It may be necessary to administer digitalis and propranolol in conjunction with pacing in order to achieve this effect A permanently implanted radio frequency pacemaker operated as necessary by the patient may be extremely useful for recurrent tachycardias [42]

3 *Re entry tachycardia and pre excitation syndrome* In both instances pacing of either the atrium or the ventricle at a near physiologic rate may not capture the rate or even if it does may not allow slowing or cessation of pacing without return to the original rhythm Rapid atrial pacing may convert the rhythm to unstable atrial fibrillation or may interrupt the circus movement [43] As the approach is not universally effective its efficacy in a specific instance should be demonstrated prior to

*American Optical Co Framingham Mass.

stablishing permanent pacing in the case of a recurrent tachyarrhythmia such as Wolff Parkinson White syndrome[44] Some patients will require the addition of small to moderate doses of suppressive drugs such as beta adrenergic blocking agents to facilitate cardiac sensitivity

In the Wolff Parkinson White syndrome it is probable that the reciprocating path ways or circus movements responsible for the tachycardia may be interrupted by the rapid stimulation While reports of termi nation of the tachycardia by a single atrial stimulus have appeared[45] a period of sev eral seconds of rapid atrial pacing is more effective at a practical therapeutic level

4 *Ventricular arrhythmias and especially tachycardias* have been successfully man aged by ventricular pacing at rates ade quate to *overdrive* and suppress the ar rhythmia[46] In the presence of intact con duction atrial overdrive is probably more effective

a The electrode may contribute to fur ther ventricular irritability by mechanical stimulation of the ventricle This is avoided by atrial stimulation

b Cardiac output is increased by atrial relative to ventricular pacing and this increase in output may assist in resolution of the etiology of the tachycardia Addi tional drug or other therapy should be directed at the heart as overdrive sup pression of tachycardia is a short term expedient

Conclusion

In an area more limited than that for ventricular pacing atrial pacing at physio logic rates or at rapid rates for short periods of time has multiple significant uses The major limitations of atrial pacing for long term use are the lack of availability of reliable atrial leads and electrodes which will function well as atrial sensors as well as stimulators Because of the simultaneous existence of atrial arrhythmia and atrio ventricular *block an A V sequential* pacer of proved reliability will undoubtedly in crease the utility and use of atrial pacing

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Annotations

Tricyclic antidepressants and cardiac disease

Cardiovascular complications following the administration of tricyclic antidepressants are well documented.[1] The most serious of these, death, was reported in association with imipramine by Kristiansen in 1961 and with amitriptyline by the Australian Drug Evaluation Committee[2] in 1965. Suspicion that the tricyclic antidepressants were cardiotoxic was increased by the number of serious adverse cardiac effects reported to the Committee on Safety of Drugs[3] by 1968 and epidemiological evidence to confirm or refute this suspicion was sought.

A hospital based drug information system described by Coull and associates, which links details of patient identification with diagnosis and drug therapy, made possible the rapid identification of all patients in the Aberdeen General Hospital who had received amitriptyline in the forty month period ending in September 1971. The number of patients identified was 864, this being the total population at risk of the adverse effect. Since, however, Kristiansen[4] had shown that patients with cardiac disease were more susceptible to cardiac side effects, detailed study was limited to patients who had cardiac disease and who had received amitriptyline in the two weeks preceding discharge from hospital or death, as it seemed unlikely that earlier discontinuation of the tricyclic antidepressant drug could be associated with subsequent death. Therefore 119 patients were the subject of further study and of these 23 patients had died. Examination of the clinical records revealed that 13 of the deaths were sudden and unexpected—i.e., death occurred within 24 hours of the onset of the terminal illness, there being no previous indication that death was imminent.

To ascertain whether amitriptyline played a role in inducing these deaths it is necessary to compare them with the deaths in a control population who did not receive amitriptyline. Since there is a very close correlation between age, sex, diagnosis and mortality rate, it is of paramount importance when looking for an event such as unexpected death that the patients should be adequately matched for these factors. In addition, as the chance of recording a death in hospital is related to the length of hospital stay, this parameter was also included in the matching criteria. It proved possible, because of the large numbers of patients in the system (120,000 patients, September 1971), to find 339 controls of the same sex, very similar age, diagnoses and period of hospitalization but who did not receive a tricyclic antidepressant. Fifteen patients died in this group, 3 of them unexpectedly, as compared with 13 in the amitriptyline group, and this difference is possibly significant (χ^2 = 1[illegible]3, p < 0·0[illegible], Singleton). The occurrence of myocardial infarction, cardiac failure and severe anemia (Hb < 70 per cent) were used to estimate the severity of the patients' cardiac disease and general condition in both groups. It was similar and the controls were therefore also well matched in these respects.

The drugs administered to the amitriptyline population and their controls were carefully reviewed. While a large number of different drugs was prescribed for each group and those who died in each group received on average more than those who lived, the overall prescribing pattern was similar. Amitriptyline was prescribed in the test group in conventional dose regimes and digoxin was the only drug in common use in both groups which had a direct cardiac effect.

The progress and treatment of the amitriptyline group and their controls was followed after discharge from hospital. A proportion of the amitriptyline patients continued to receive the drug and it was of interest to note that the drug had been prescribed for some of the controls, reinforcing the assumed adequacy of the control population. The ultimate prognosis in terms of mortality rate in the original test and control groups with or without amitriptyline subsequently proved to be remarkably similar and suggests that amitriptyline may have precipitated by a number of months or years an inevitable sudden death.

The occurrence of sudden unexpected death was also investigated in 88 patients without cardiac disease who received amitriptyline and a carefully matched control population. One sudden unexpected death attributed to a cerebrovascular accident occurred in the amitriptyline group and none in the controls. Imipramine is related pharmacologically to amitriptyline and it therefore seemed possible that imipramine might also be cardiotoxic. Four sudden unexpected deaths occurred in 87 cardiac patients receiving imipramine compared with 2 in a control group. These numbers are too small to permit valid conclusions but it seems possible that imipramine may be associated with unwanted cardiac effects and this is now the subject of further study.

The investigation of major adverse drug reactions such as death poses a difficult problem for it is not easy to justify prospective controlled clinical trials of potentially lethal drugs In this situation the comparison of retrospective data from a hospital drug information system for two groups of patients adequately matched but for the administration of the suspected drug has been valuable and the suspicion that amitriptyline may be associated with sudden unexpected death has been confirmed in a population with pre existing cardiac disease While such epidemiological investigations can contribute to the safer and more rational use of drugs they can never establish with certainty a cause and effect relationship and detailed pharmacological investigation is necessary Nevertheless even if the pharmacological basis is not fully understood in view of the serious nature of the adverse effect in question the results suggest that amitriptyline should be prescribed with caution in patients with cardiac disease and that similar pharmacological agents such as imipramine merit further investigation

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Hemoglobin, plasma lipids, and coronary heart disease

During recent years several so called risk factors for coronary heart disease (CHD) have been identified—and intensively discussed Many seem to have used the word risk factor to denote not only a definite *risk in* the individual patient but also a direct *pathogenic* influence of the factor itself Clearly a *factor* the presence of which is associated with increased rate of development of CHD may on one hand *cause* this development but might on the other only be a parallel or associated phenomenon without direct pathogenic importance In spite of the fact that a large number of risk factors for CHD have been identified little is known about the way in which they are associated with the development of CHD Much more research is needed to clarify these matters One approach is to study the possible interrelationship between risk factors

The first large prospective study to identify risk factors was the Framingham study [1] which has been followed by similar investigation aimed at identifying risk factors One of the more recent ones is the Stockholm Prospective Study [2,3] which has confirmed previous findings of elevated serum cholesterol elevated blood pressure (systolic as well as diastolic) elevated hemoglobin values and smoking as risk factors for CHD and has added two others elevated fasting serum triglycerides and erythrocyte sedimentation rate The linear relationship found between plasma cholesterol and triglycerides respectively and the rate of development of new events of CHD is shown in Figs 1 and 2

High hemoglobin or hematocrit (packed cell volume) has been identified as a risk factor for CHD [4,5] As it has not been a matter of extreme values and as it is known—i e from polycythemic conditions—that the rheological properties of the blood are not influenced until the hemoglobin values reach very high levels (above 20 Gm per 100 ml) it has been difficult to understand the meaning of these findings A recently reported study [6] might throw some light on the problem

As already mentioned in the Stockholm Prospective Study plasma lipids (cholesterol and triglycerides) were identified as risk factors for CHD but so were high hemoglobin values

A statistical analysis of a possible relationship between plasma lipids and hemoglobin in the Stockholm Prospective Study has now been performed *It was shown that there exists a weak but significant* ($P < 0.01$) positive correlation between on one hand hemoglobin and on the other plasma cholesterol or plasma triglycerides (Table I) This correlation has previously been found for cholesterol in anemic women but not in healthy women with normal hemoglobin values and not in healthy men No such correlation has earlier between

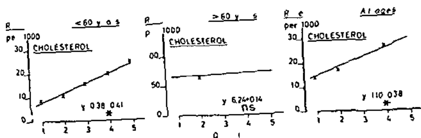


Fig 1 Linear regression analysis of the rate of new events of CHD in relation to plasma cholesterol quintiles

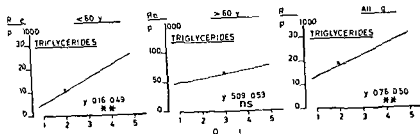


Fig 2 Linear regression analysis of the rate of new events of CHD in relation to plasma triglyceride quintiles

plasma triglycerides and hemoglobin Also partial correlation coefficients keeping age constant clearly show that the correlation exists regardless of age

It is of interest that in our material the differences in cholesterol values corresponding to variations in hemoglobin within the normal female range (11 to 14 Gm per 100 ml) were of the same order of magnitude as the variations found by Elwood and associates[7] in his material of anemic women (or 6 mg per 100 ml for each gram of hemoglobin per 100 ml blood) (Table I)

The variations in serum lipid values with the hemoglobin levels may of course be coincidental and largely independent of each other They could however also be explained by changes in plasma volume If we assume that in a woman the blood volume remains unchanged as the hemoglobin decrease from 14 Gm to 11 Gm per 100 ml the packed red cell volume would decrease from 40 to 32 per cent and consequently the plasma volume would *increase* from 60 to 68 per cent If the total plasma pool of lipids would remain unchanged the concentration of cholesterol would diminish from an assumed 250 to 220 mg per 100 ml and of triglyceride from 1 10 to 0 97 mmole/L that is a decrease with 30 mg 100 ml and 0 13 mmole/L respectively From the regression equations (Table I) the corresponding figures can be calculated to be 18 mg/100 ml for cholesterol and 0 13 mmole per liter for triglycerides Similar calculations with similar results may be carried out for men Although many assumptions are involved in such calculations—and great standard errors occur in the equations—simple changes in plasma volume might at least in part account for the positive correlation between hemoglobin and plasma lipid It should be emphasized that this is a theory or speculation today without any proof There are of course also other ... such as increased synthesis of

Table I Regression equation between hemoglobin values (x) and serum lipid levels (y) in men and women (aged 20 to 54 years)

Variables	*Regression equation*
Men (n = 1 190)	
Hemoglobin–triglycerides	y = 0 124x − 0 262
Hemoglobin–cholesterol	y = 4 75x + 208 0
Women (n = 895)	
Hemoglobin–triglycerides	y = 0 044x + 0 605
Hemoglobin–cholesterol	y = 6 00x + 198 5

porphyrins and lipoproteins as recently suggested by Lees and colleagues[8]

However irrespective of why hemoglobin is positively correlated to both plasma cholesterol and triglycerides the correlation may in part explain why a high hemoglobin value has been found to be a risk factor for CHD The difference in mean hemoglobin values between the lowest and highest quintile in the Stockholm Prospective Study was approximately 4 0 Gm per 100 ml for men The regression equations in Table I then predict that the cholesterol and triglyceride levels (on the average) would be 4 0 4 75 = 19 mg per 100 ml and 4 0 0 124 = 0 50 mmole per liter *higher* in the top than in the bottom hemoglobin quintile

The rate of CHD had increased from 30 per 1 000 in the lowest to 44 per 1 000 in the highest quintile For men 50 to 70 years of age the average span of quintiles 2 3 and 4 was for cholesterol 31 mg per 100 ml and for triglycerides 0 34 mmole per liter

The regression equations (Figs 1 and 2) thus predict—in this region—that the rate of new events of CHD will increase with 0 12 per 1 000 and 0 15 per 1,000 for an increase of 1 mg per 100 ml of cholesterol and 0 01 mmole per liter of triglycerides respectively Applying these figures to the above mentioned values of 19 mg per 100 ml and 0 50 mmole per liter they would correspond to an increase in the rate of CHD events of 2 3 and 7 5 respectively or together 9 8 per 1 000 This value arrived at from calculations using regression equations with statistical as well as biological limitations is fairly close to the actual difference of 14 per 1 000 between the bottom and top hemoglobin quintile Thus hemoglobin as a risk factor for CHD might be explained not by the high hemoglobin value itself but by the fact that the *plasma lipids* are increased as well

It should finally also be stressed that so called risk factors for CHD to a large extent covariate and are difficult to treat as single phenomena As an example we can mention the erythrocyte sedimentation rate (ESR) which was found to be a risk factor It has long been known that ESR and hemoglobin values are closely related (for discussion see Ref 8) Furthermore recent studies have indicated that the ESR is closely associated also with other risk factors Thus studies on the Stockholm Prospective Study material have shown that there exist positive correlations between elevated ESR values and elevated plasma lipids (cholesterol as well as triglycerides[10]) and that elevated ESR values are found in persons with asymptomatic hyperlipidemia[11] The final answer to the question of the importance of elevated hemoglobin or erythrocyte sedimentation values as pathogenetic or non pathogenetic risk factors for CHD must await the results of further studies

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Aspirin-like drugs and prostaglandins

The aspirin like drugs are a diverse group of compounds all of which possess in some measure the anti pyretic anti inflammatory and analgesic actions which are characteristic of aspirin

Aspirin itself was introduced into clinical medicine in the late 1890 s but decoctions of the bark or leaves of willow trees which contain derivatives of the parent compound (salicylic acid) have been valued for their medicinal properties for centuries The leaves are bitter reads one account and the *Hottentots and the Xosas* use them in rheumatic fever [1] Yet despite their long history and wide spread use (it is estimated that 4 000 million aspirin tablets are consumed each year in England alone) the question of how the aspirin like drugs exerted their therapeutic effect remained unanswered Al though they were known to interfere with a wide variety of cellular enzymes no convincing relation

hip could be established between the experimental findings and the observed clinical actions. This situation changed in 1971 when a group of workers at the Royal College of Surgeons of England, led by J. R. Vane, discovered that aspirin-like drugs inhibited the biosynthesis of prostaglandins.[1-4] Prostaglandins are a family of long-chain fatty acids which possess an unusually wide spectrum of biological activity. The capacity for generating these extremely potent substances is apparently shared by all tissues of the body, and at the time of this discovery there was some evidence suggesting that prostaglandins participated in the pathogenesis of fever and inflammation. Thus, as Vane pointed out, inhibition of prostaglandin synthesis might explain the mode of action of the aspirin-like drugs. Today, almost two years later, all the available evidence supports this conclusion.[5,6]

Almost all the aspirin-like drugs have been found to inhibit the enzyme system which synthesizes prostaglandins (prostaglandin synthetase). The steroidal anti-inflammatory drugs and the narcotic analgesics, which have some similar therapeutic actions, are ineffective, as are many other drugs which do not have any aspirin-like actions, and this suggests that inhibition of prostaglandin synthesis is a property peculiar to this class of drugs. In man, a single dose of salicylates or indomethacin is sufficient to reduce the synthesis of prostaglandin by an easily detectable amount, and treatment with therapeutic doses of these drugs for two or three days results in a very pronounced inhibition.

There are several lines of evidence that point to the involvement of prostaglandins in inflammation: prostaglandins are found in inflammatory exudate and, if injected intradermally, reproduce many of the salient features of the inflammatory response. Furthermore, the delayed phase of inflammation, which is selectively suppressed by aspirin, is the phase in which prostaglandins appear. The relative therapeutic activity of several well-known anti-inflammatory drugs fits well with their anti-PG synthetase activity, and the concentrations required for inhibition are within the plasma levels achieved by these drugs during treatment. With regard to the antipyretic activity of these drugs (a central action), prostaglandin has been detected in the CSF of cats during fever, and when this was reduced by the administration of aspirin-like drugs there was also a concomitant decrease in the concentration of prostaglandin. Conversely, when injected into the CSF of animals or systematically into man, prostaglandins cause a fever which is not blocked by aspirin-like drugs.

The foregoing findings are consistent with the notion that the prostaglandins are causal agents in inflammation and fever, and thus inhibition of synthesis could adequately account for two of the three therapeutic effects of these compounds—but what of their analgesic activity? At first this was more difficult to accommodate within the theory. These drugs possess only a weak analgesic action and are only effective against certain types of low-intensity pain. It was known that prostaglandins were painful when injected into man and some animals, but only in much larger concentrations than would be likely to occur in tissues. However, when continuously infused subdermally in doses too small to cause overt pain, the prostaglandin caused a long-lasting hyperalgesia—an increased sensitivity to mechanical stimulation as well as to other endogenous substances such as histamine or bradykinin. It seems from these studies that prostaglandins released, say, from the site of a local lesion could sensitize afferent pain fibers to other mechanical or chemical stimuli. Thus the analgesic action of the aspirin-like drugs could be attributed to the removal of this facilitating effect, and this would explain why aspirin is only a weak analgesic.

The aspirin-like drugs have a number of unexplained side-effects such as gastric irritation, nephrotoxicity, and disturbances in collagen metabolism, and there are already several lines of evidence which link these effects with their anti-PG synthetase activity. For example, prostaglandins could be released from the gastric mucosa during the churning of the stomach contents after a meal, and since some of the prostaglandins are known to be inhibitors of gastric acid secretion, a negative feedback loop has been postulated which controls the pH of the gastric contents. If this loop were "broken" by the administration of prostaglandin synthesis inhibitors, acid secretion could increase, leading perhaps to irritation or erosion of the gastric mucosa, a side-effect often associated with these drugs.

The discovery that the aspirin-like drugs inhibit prostaglandin synthesis has given the clinician an insight into the nature as well as the treatment of pain, fever, and inflammation—but it has also been of value to the physiologist who wishes to assess the function of the prostaglandins in the normal body and also to the enzymologist who wishes to learn more about the mechanism of synthesis of these fatty acids.

One apparent anomaly in the hypothesis has recently been resolved with interesting consequences: paracetamol (acetaminophen, APAP), an aspirin-like drug which has analgesic and antipyretic but no anti-inflammatory actions, was inactive against the prostaglandin synthetase prepared from peripheral tissues such as skin or spleen, against which the standard drugs were active. Did it work by a different mechanism? The only alternative appeared to be that paracetamol exerted its actions only within the CNS. When a prostaglandin-synthesizing system was prepared from brain tissue it was found that the drug was indeed very active against prostaglandin synthesis.[7] This finding suggests that the enzymes responsible for prostaglandin biosynthesis in the various tissues of the body may be differentially sensitive to inhibition by the aspirin-like drugs. It may even be possible to produce drugs of this type which have selective actions on certain organs or which are free from unwanted side-effects.

In conclusion, it is pertinent to ask what relevance these findings have to cardiology. This is difficult to answer at the moment: prostaglandins have a positive inotropic effect on the myocardium of the isolated heart and increase the cardiac output and coronary flow in man and animals. More than one study suggests that they may be involved in autoregulation of coronary blood flow.[8] At the time of writing, however, no disease condition has been

specifically associated with abberant prostaglandin production by the heart

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Surgical versus medical management of coronary heart disease

Comparisons of the operative risks of medical and surgical management of ischemic heart disease are summarized in Table I No surgeon will ever top the surgical risks of the cardiologists Therefore the evaluation of the surgical treatment is reduced to the answers to two questions namely

1 What is the survival rate when surgery is employed?

2 Do the benefits of surgery justify the risks suffering and co ts? If so where is the evidence?

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Table I Comparisons of operative risks of medical and surgical management of ischemic heart disease

	Treatment	
	Surgical	*Medical*
Operative mortality	4 to 25 + %	Zero
Operative complications early and late (myocardial infarction hemorrhage infection thromboembolism etc)	25%	Zero
Total cost of operation	$8 000 to $35 000 +	Zero
Closure of shunt	25% in 2 years	Zero
Cures	Zero	Zero
Operative pain and suffering	100%	Zero
Operative psychic stress to patient and family	100%	Zero
Survival time	Unknown	Known

Letters to the Editor

Echocardiographic studies of mitral valve

To the Editor

I was very interested to read the article by Millward McLaurin and Craige[1] in a recent issue of THE JOURNAL (AM HEART J 85 413 1973) I would like to make the following comments on their article

1 Measurements of mitral valve excursion (MVE) are wrong these were measured between points D and E on the mitral valve echogram and they should be measured between points C and E the most posterior and the most anterior points of the anterior mitral valve leaflet movement The authors compared their measurements to those done by Wharton and Bescos[2] In Wharton and Bescos paper (p 348) it is well documented that their measurements were done between points C and E (Fig 5 postop LCG) Most measurements of the mitral valve excursion are based today on the distance between C and E[3] and not D and E as done by the authors From the above it is understood that all of Millward McLaurin and Craige s measurements of the mitral valve excursion and the numbers they compared their measurements to were wrong since the measurements are based on wrong criteria

2 The authors state that in 16 of 17 patients with congestive cardiomyopathy (CCM) the mitral valve echogram was abnormal in that the two mitral valve leaflets never completely approximated one another during ventricular systole This is not documented in their echocardiograms

2A In Fig 2 (p 414) only the anterior mitral leaflet is demonstrated during diastole Unless both leaflets are well demonstrated during diastole no conclusions as to the posterior leaflet s movements during systole can be drawn From this echogram alone it seems that there is some abnormal systolic *anterior* movement of the anterior mitral leaflet documented in case with IHSS but seen in some patients with the mid systolic click-late systolic murmur syndrome at the upper part of the anterior mitral leaflet near its ring

2B In Fig 4 (p 417) (note the description of Fig 5 belongs to Fig 4 and vice versa) in the third echogram (B W) it is well demonstrated that the two mitral leaflets do merge into one line during systole—the other parallel line could most probably be prevented by tilting the transducer It seems according to our experience as well as to others[4,5] that systolic separation of the mitral leaflets without posterior displacement of one or the other leaflet is not diagnostic of mitral insufficiency due to papillary muscle dysfunction In eight of our babies with severe CCM six of whom had and two of whom did not have mitral regurgitation no correlation could be found between mere systolic separation (without systolic posterior displacement of the mitral leaflet) and mitral insufficiency In fact systolic separation of the mitral leaflets without posterior displacement can be found in many normal individual

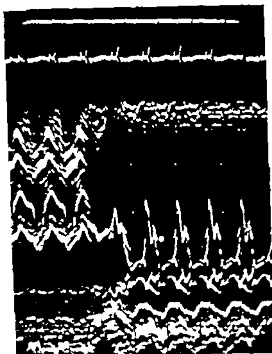


Fig 1 Echocardiogram of a 13 month old girl with severe congestive cardiomyopathy The transducer was tilted from the aorta (left side of the picture) to the mitral valve and the left ventricle while the picture was taken The left ventricle is very dilated the mitral valve apparatus is dislocated posteriorly the septum is dislocated anteriorly The baby died and the autopsy showed a very dilated left ventricle with endocardial fibroelastosis

3 The authors state that All of the patients with acute mitral regurgitation due to ruptured chordae tendinae showed systolic separation (p 415) In Fig 5 (p 417) case B G shows only systolic separation (which could be normal) but no posterior systolic displacement of any of the leaflet Thus this echogram is not necessarily diagnostic of papillary muscle dysfunction

4 One important finding which is not mentioned by the authors but is seen in two of their echograms (patients J M and B W Fig 4) is the posterior dislocation of the mitral valve apparatus in patients with CCM In our material all eight patients with CCM demonstrated this phenomenon The mitral valve leaflets are seen very close to the posterior wall of the dilated left ventricle away from the interventricular septum This can be best documented by moving the transducer from the aorta to the left ventricle The mitral apparatus instead

of being continuous with the posterior wall of the aorta is pushed posteriorly The interventricular septum which in the normal is continuous with the *anterior wall* of the aorta is pushed in anterior direction (Fig 1)

This echographic picture is diagnostic of CCM and demonstrates severe dilatation of the left ventricle

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Reply

To the Editor

We appreciate the opportunity to comment on some of the questions raised by Dr Glaser in his letter referring to our article published in the March 1973 issue of the AMERICAN HEART JOURNAL

1 The anterior motion of the closed mitral valve during systole (C to D on the echocardiogram) is thought to be secondary to motion of the mitral annulus[1] and does not represent independent motion of either anterior or posterior mitral valve leaflets It seems to us that in assessing excursion of the anterior leaflet in early diastole a more appropriate convention is to measure points D to E It is probably not justifiable to compare our results with those of Wharton and Bescos[2] since they made their measurements in a different way but we disagree that our measurements are wrong The method we used is clearly stated The technique and results are internally consistent and the relationship of early diastolic excursion of the anterior leaflet among the various patient groups is as stated in our manuscript

2A We do not believe it to be possible to state which leaflet is prolapsing in Fig 2 The temporal relationship of the leaflet separation to the systolic click and subsequent murmur recorded phonocardiographically was very precise and reproducible We would agree that the echo is not typical of the posterior bowing motion more commonly seen[4]

2B In Patient B W the mitral leaflet echoes do come into contact in systole but separate signals representing anterior and posterior leaflets remain apparent It is true that multiple echo signals usually from the anterior leaflet can be produced by tilting the ultrasonic transducer so that the valve leaflet is not perpendicular to the full beam of ultrasound In view of this potential for artifact we would agree that multiple echoes are not necessarily diagnostic of leaflet prolapse and thank Dr Glaser for re emphasizing this fact Nonetheless we were impressed and in fact stimulated to do the study by the consistency with which both mitral valve leaflet echoes could be obtained in systole in patients with CCM Although the use of M mode scans and strip chart recorder has increased our ability to obtain good echograms of both mitral leaflets in other patients it has remained true that a clear representation of both leaflets with multiple systolic echoes is most easily obtained in patients with CCM Systolic separation of the leaflets is clearly not a specific sign of papillary muscle dysfunction although in our opinion this is the most tenable hypothesis to account for mitral regurgitation in CCM

3 The first beat of the echogram in patient G V clearly shows both anterior and posterior leaflets The upper systolic line is continuous with the posterior leaflet echo seen in diastole

4 In most adults the posterior mitral valve leaflet is very close to the posterior wall of the LV the anterior leaflet is somewhat variable in its relationship to the IV septum We thank Dr Glaser for pointing out the interesting phenomenon seen in his experience with children We think it is pertinent to mention that a lack of continuity of the aorta and mitral apparatus or posterior dislocation of the mitral apparatus is most frequently seen in cases of double outlet RV Although the echocardiogram of Fig 4 shows the mitral valve leaflets to be close to the posterior surface of the heart definite statements regarding true dislocation of the mitral apparatus require continuous scanning as pointed out by Dr Glaser We are currently using strip chart M mode scanning techniques to re evaluate adult patients with dilated left ventricles in hopes of detecting changes in the geometric relationship of various cardiac structures in dilated hearts It is our current belief that such alterations will depend more on changes in the position of the IV septum and LV posterior wall the semilunar and atrioventricular valves being attached to the rather unyielding fibrous skeleton of the heart

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megakaryocyte phenomenon and a control of heparin with the Dale and Laidlaw Coagulometer makes heparin prophylaxis understandable and as in my on going study em nently succes ful

I will agree with Dr O Brien that we have much to learn about the actual factors which lead to thrombosis This I am ure will become evident when we di cover just what is derived from our fresh platelets which may suddenly be liberated from the pulmonary megakaryocytes to produce the hyper coagulable state and thrombo is

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Heparin and venous thrombosis

To the Editor

I am quite di turbed by the editorial appearing in the April issue of THE JOURNAL by Dr J R O Brien (AM HEART J 85 435 1973) on the question of heparin and venous thrombosis Dr O Brien merely repeats what he had written in the March 1973 i ue of *Modern Concepts of Cardiovascular Disease* In both instances he finds it d fficult to comp ehend the reason for the uccess of small doses of subcutaneous heparin in the prevention of venous thrombo is and embolism in the operative patient It is a program first ad ocated by me in 1962 and not by Mr Kakkar who merely called it low dose heparin and altered the heparin chedule ightly My program continues ucce fully and I still prefer to designate it as small dose heparin prophy laxis[1] Dr O Brien concedes that heparin is effective according to Mr Kakkar and other English investi gators [4] who had the opportunity den ed us here (F D A *restriction*) in evaluating their patients for deep leg ve n thrombo i with the I[125] fibrinogen uptake te t but according to his platelet and other studies *for the wrong reasons* This asses ment lead only to greater confu ion in under tanding the rationale and w ll d courage the use of heparin prophylaxis in the great *need of prevention of fatal* thromboemboli m However there is a rationale for the ubcutaneou mall dose hepar n routine which prompted the program *initiated by me It* i based on my earl er observation on the long over *looked* phenomenon of the pulmonary megakaryocytes This I expla ned fully n *an earlier report to* the AMERICAN HEART JOURNAL in December 1970[9] *and other* earl er pul l cation [•] But curiously enou h Dr O Brien and the Briti h investigators Kakkar and colleagues Gordon Smith and asso ciate Nicolaides *and co-worke* s and Gallus and colleagues fail to mention this rationale It i Mr Kakkar especially who offers no rationale and his use of low dose subcutaneous *heparin All* admit that most laboratory te ts[13] are insen tive in de termin ng such rat onale as to t me and dose and therefo e are valueless in establ *hing uch routine* Howe er in my hand the modified Dale and Laidlaw Coagulometer has proved to be sen itive enou h reproducit le and essential *to my success* Thus I find that an appreciation of the pulmonary

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Reply

To the Editor

No bibliography is ever complete or satisfies everybody. I apologize for not including a reference to Dr. Sharnoff's well known pioneer work with heparin. I omitted this because it is mentioned in the references I quoted and because even though his studies refer to clinical disease. I felt the recent work using Iodine 125 fibrinogen in a series of properly controlled studies gives greater precision and makes an even better case for the use of low/small dose heparin—providing that the incidence of clinical disease runs parallel to the incidence of thrombosis diagnosed by this test.

Personally, I would not recommend the modified Dale and Laidlaw coagulation time nor do I think there is universal acceptance that the rationale of this treatment is based on the prevention of a hypercoagulable state due to the liberation of platelets from pulmonary megakaryocytes. But these are matters of opinion.

In the meantime, another valuable study supporting the beneficial effects of heparin (and quoting Dr. Sharnoff's papers) has recently appeared.[1]

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Book reviews

CLINICAL PATHOLOGIC CORRELATIONS 2 Jesse E Edwards Guest Editor CARDIOVASCULAR CLINICS Albert N Brest Editor Philadelphia 1973 F A Davis Company 331 pages

The publications of Cardiovascular Clinics continue to be of high quality They are all clinically oriented and therefore should interest practicing physicians This issue on the CPC is of considerable value to those who wish to learn the relationship of pathology to the clinical manifestation of heart disease The diseases presented of broad interest reflect the efforts of authorities in cardiology Such illnesses as hypertension ischemic congenital cardiomyopathy and surgical forms of heart disease are discussed Each chapter is presented as a clinical paper with excellent illustrations and bibliography This is another excellent contribution to cardiology Jesse Edwards has produced a useful book for the practicing physician

ADVANCES IN MICROCIRCULATION Vol 5 H Harders Editor Basel 1973 S Karger AG 106 pages

This is another excellent publication on the microcirculation Volume 5 of Advances in Microcirculation is concerned with qualitative and quantitative analysis blood rheology intravascular and extravascular morphologic phenomenon in cat skeletal muscle low flow states and the microcirculation of wound healing These are all extremely important subjects which are discussed clearly and are well illustrated The authors did not review each field thoroughly however They selected aspects of recent advances which they considered most important and interesting Those who are studying the microcirculation will want to own this publication

THE UROKINASE PULMONARY EMBOLISM TRIAL American Heart Association Monograph No 39 Arthur A Sasahara M D Chairman New York 1973 The American Heart Association Inc 108 pages $4 00

This paperback publication of a special issue of the American Heart Association summarizes studies of the value of urokinase in the management of pulmonary embolism The design and results of the study should be primarily of research interest This complex investigation resulted in supporting the benefit of anticoagulant therapy for patients with pulmonary embolism in the prevention of reoccurrence This reviewer is of a strong opinion that an ideal anticoagulant or fibrinolysin is yet to be produced Those interested in urokinase studies will find the report to be worthy of careful evaluation Subscribers to *Circulation* already own a copy as a supplement to their subscription to the Journal

Books received

GALAXIES OF LIFE Edited by Stanley Krippner and Daniel Rubin New York 1973 Gordon and Breach 182 pages

RESEARCH COMMUNICATIONS IN CHEMICAL PATHOLOGY AND PHARMACOLOGY Vol 5 Suppl 1 January 1973 Edited by Richard J Kones M D New York 1973 PJD Publications Ltd 84 pages

HERZINFARKT KORONARTHROMBOSE UND AKUTER KORONARTOD DES MENSCHEN By Franz Buchner Munchen Berlin Wien 1973 Urban und Schwarzenberg 178 pages

Announcements

Symposium on nutrition

The University of Texas Health Science Center at Houston Division of Continuing Education and the Texas Medical Center Inc. announce the Texas Medical Center s Symposium on the Application of Nutrition in the Health Sciences to be held in Houston Texas on February 8 and 9 1974 Participating in the symposium will be known investigators in the field of nutrition

For further information please write The Office of the Director The University of Texas Health Science Center at Houston Division of Continuing Education P O Box 20367 Houston Texas 77025

Conference on cardiac diagnosis and therapy

The Oklahoma Heart Association Colorado Heart Association and the Colorado Society for Cardiovascular Medicine are sponsoring a conference entitled 'Dilemmas in Cardiac Diagnosis and Therapy —Circa 1974 to be held at Snowmass Resort Aspen Colorado on March 21 through 23 1974 Featured speakers will be Stephen Epstein M D, Chief of Cardiology Section National Heart Institute Robert J Hall M D Medical Director Texas Heart Institute and W Proctor Harvey M D Professor of Medicine Georgetown University School of Medicine Also on the program are a distinguished faculty of Oklahoma and Colorado physicians in a series of six sessions emphasizing current problems in the diagnosis and management of common cardiovascular diseases Registration fee for the conference is *$75 00* A variety of lodge and condominium accommodations are available Deadline for housing reservations is January 1 1974 Early application is advisable because of limited registration For further information contact Colorado Heart Association 1375 Delaware Street Denver Colorado 80204 telephone (303) 623 3217

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